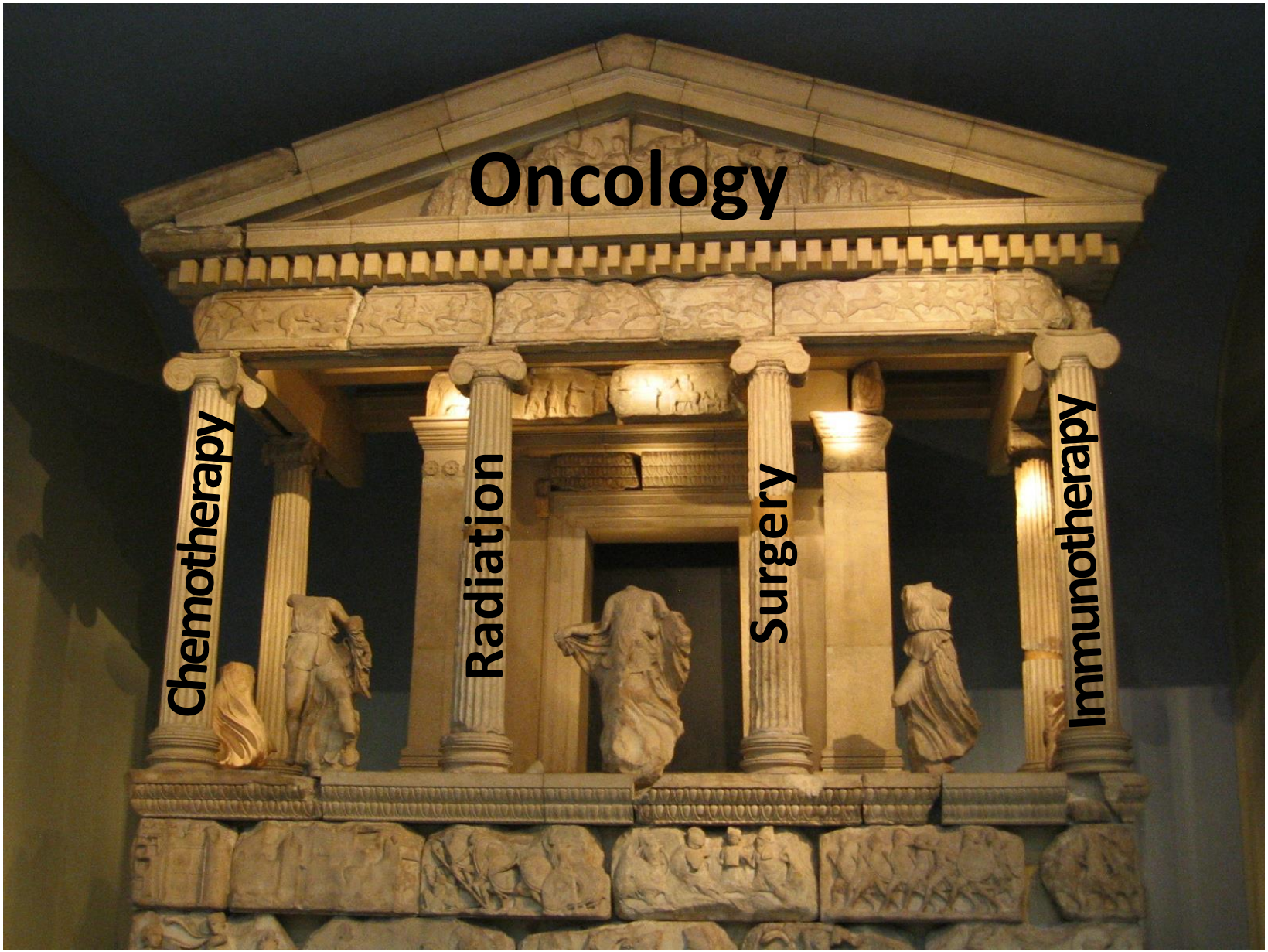
Immune Checkpoint Blockade

NCI CCR TRACO
Stephanie L. Goff, MD, FACS
September 20, 2021

Objectives

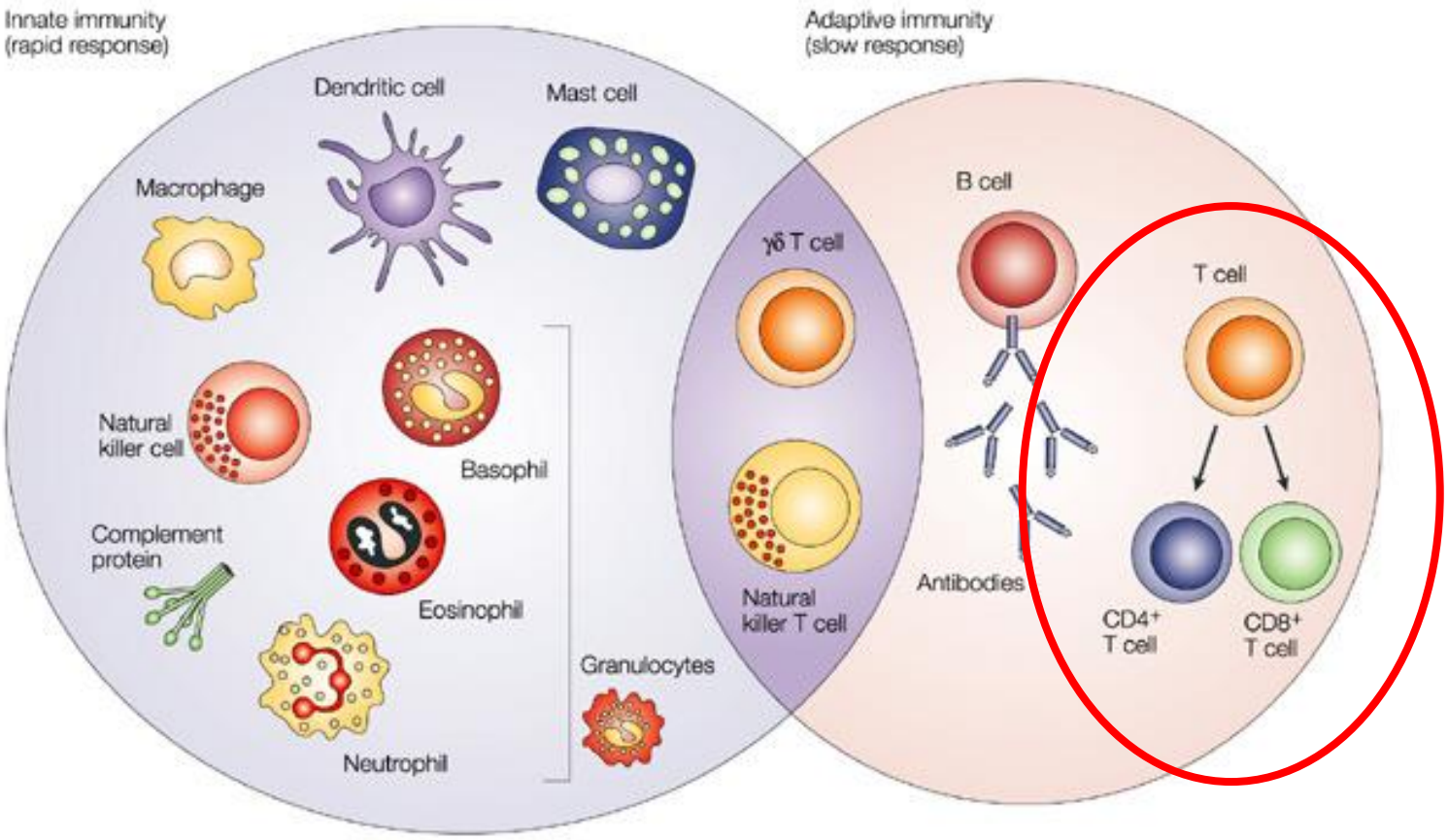
- The basics of cancer immunotherapy
- Mechanism of action of checkpoint blockade
- Early clinical experience and the discovery of immune related adverse events
- FDA approvals for metastatic melanoma
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
- Milestones in development
- Experimental Questions


Oncology
Chemotherapy
Radiation
Surgery
Immunotherapy

Cancer Immunotherapy

1. Nonspecific stimulation of immune reactions
    a) Stimulate effector cells
    b) Inhibit regulatory factors (checkpoint blockade)
2. Active immunization to enhance anti-tumor reactions (cancer vaccines)
3. Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)

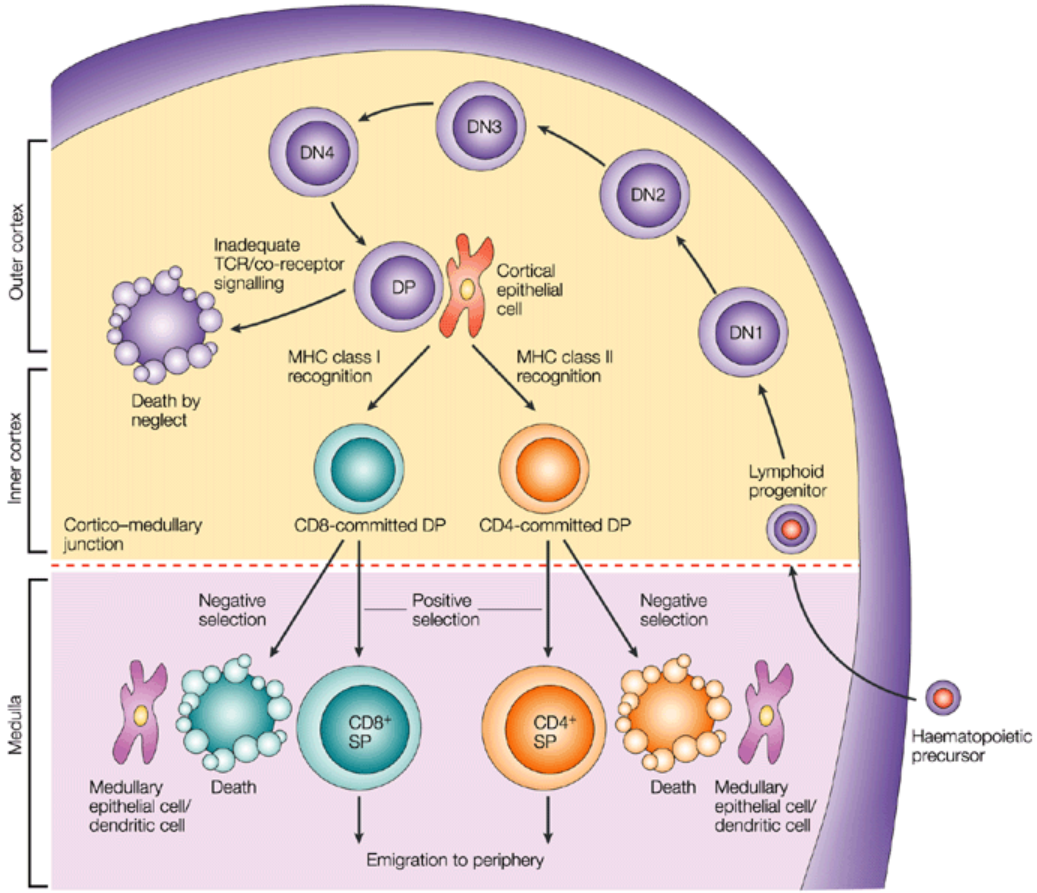
Cells of the Immune System



Dranoff 2004

- Checkpoint blockade primarily affects T cells

T cell “birth”

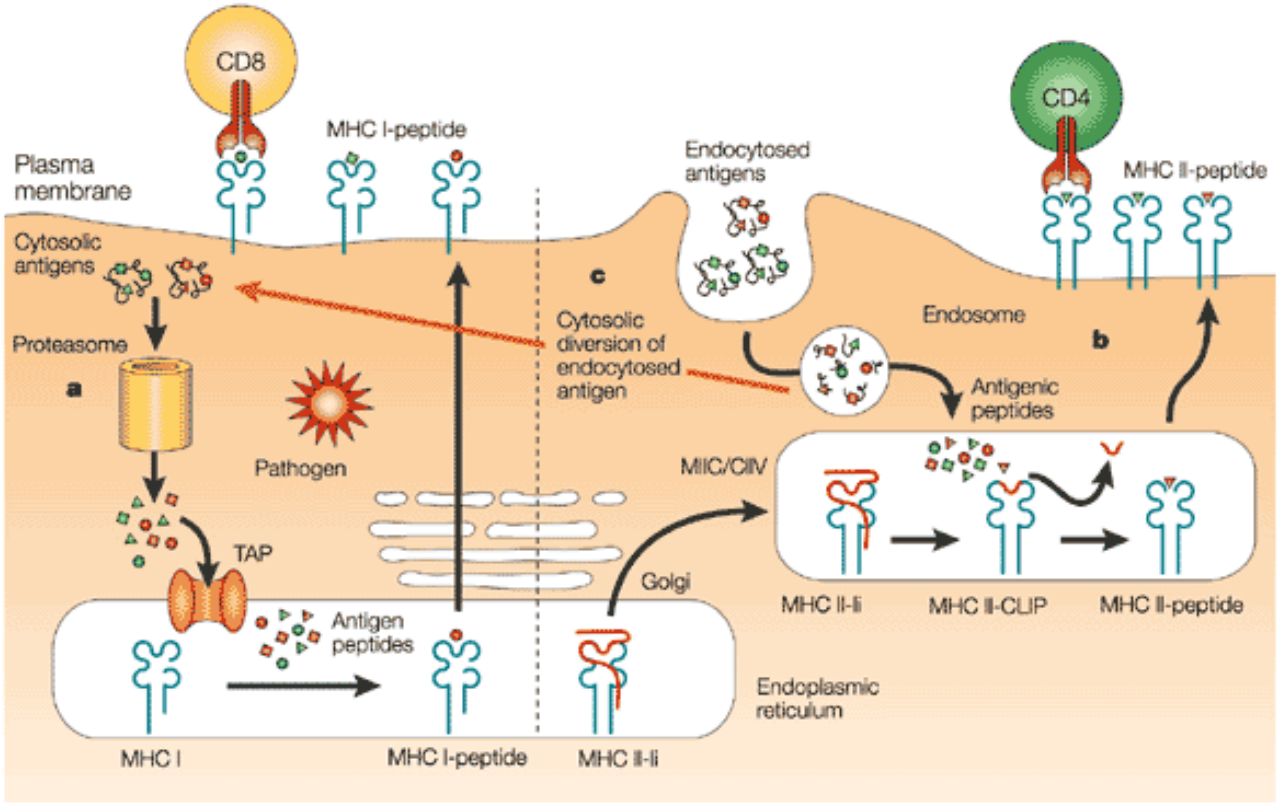


Nature Reviews | Immunology

Germain 2002

- Builds a repertoire of T cells
- ~$4x10^{11}$ circulating in an adult human

T cell activation

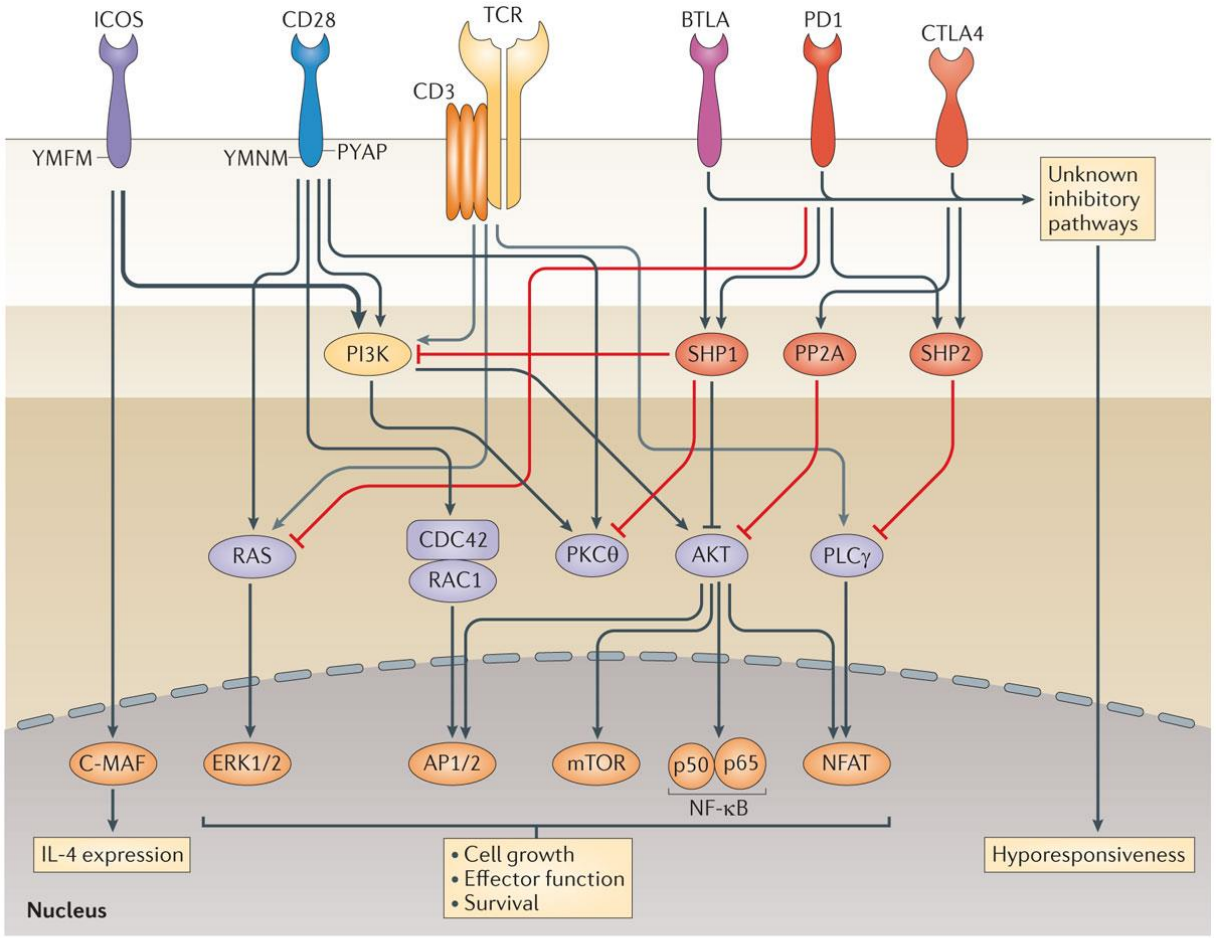


Nature Reviews | Immunology

Heath 2001

- Signal 1: Specificity
- TCR engages antigen in context of MHC

T cell activation

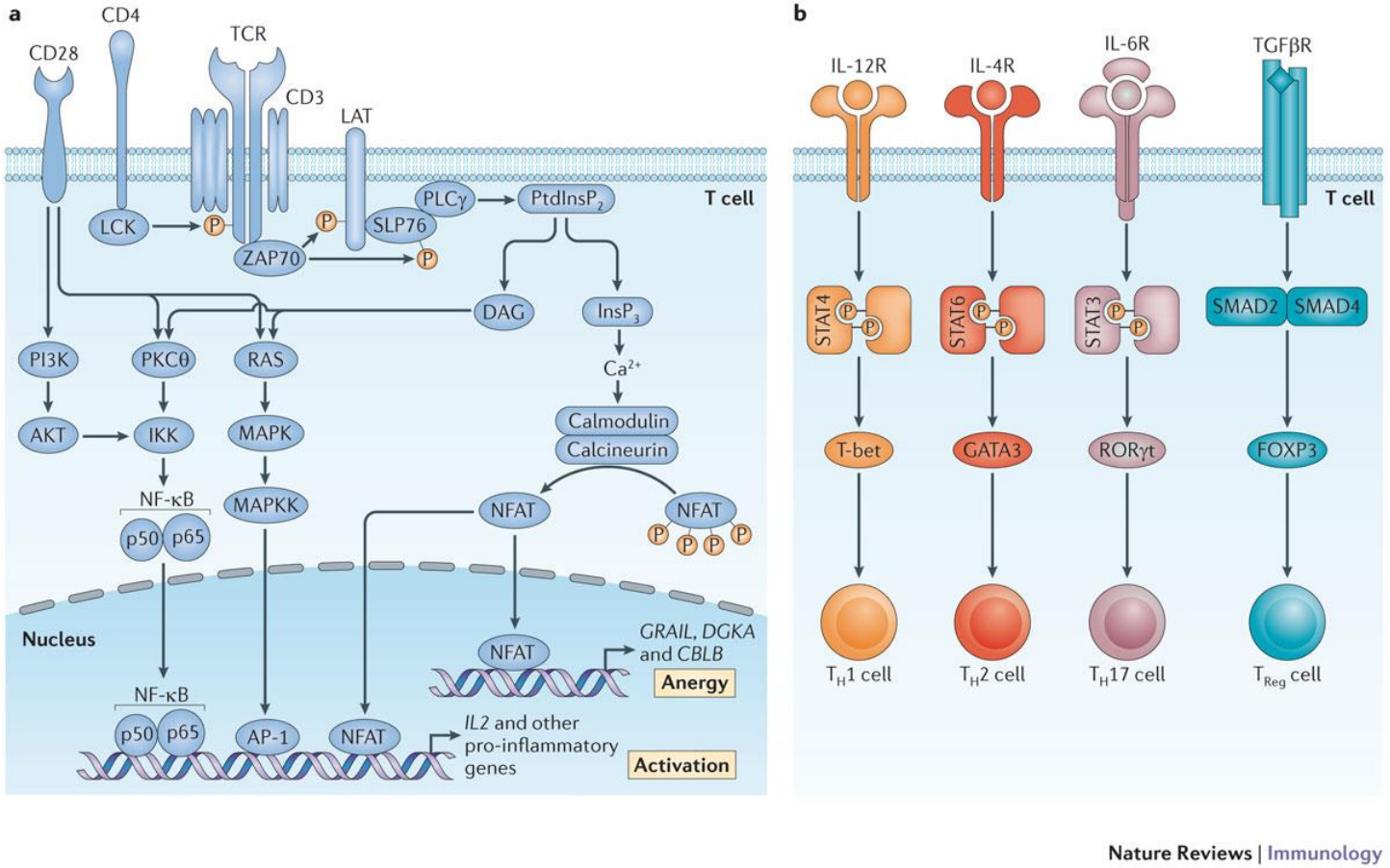


Chen 2013

Nature Reviews | Immunology

- Signal 2: Activation vs. Anergy
- Costimulatory molecules

T cell activation



Pollizzi 2014

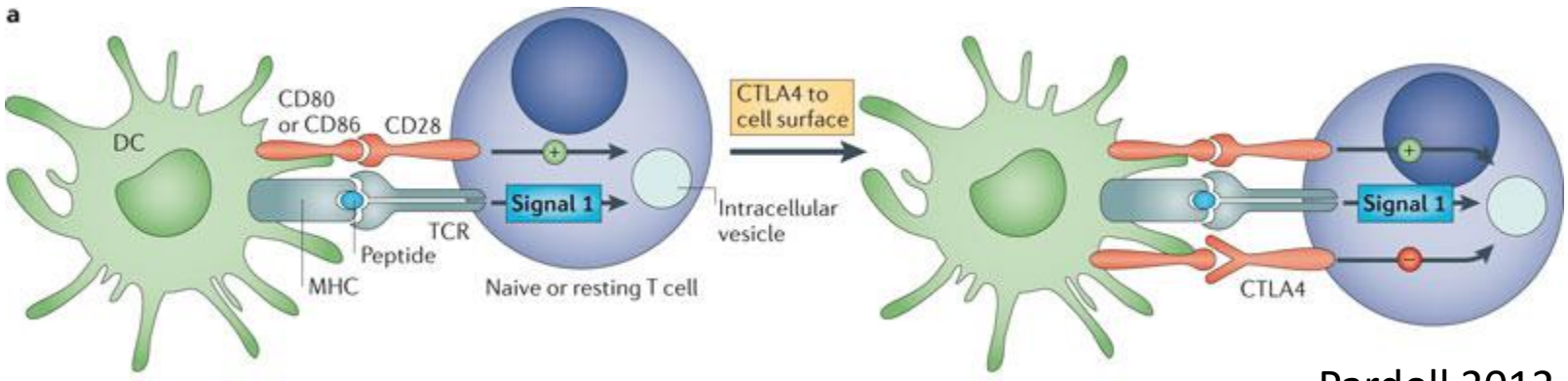
- Signal 3: Polarization
- Dependent on cytokine profile of the microenvironment

The role of Signal 2 checkpoints

- Immune checkpoints promote self-tolerance
  - Initial response to antigen occurs primarily in secondary lymphoid organs (lymph nodes, tonsils, spleen, Peyer's patches, mucosa associated lymphoid tissue)
- Immune checkpoints limit "collateral damage"
  - Effector recognition in peripheral tissue/tumor

- For cancer immunotherapy, checkpoints create opportunities to break tolerance to self-antigen

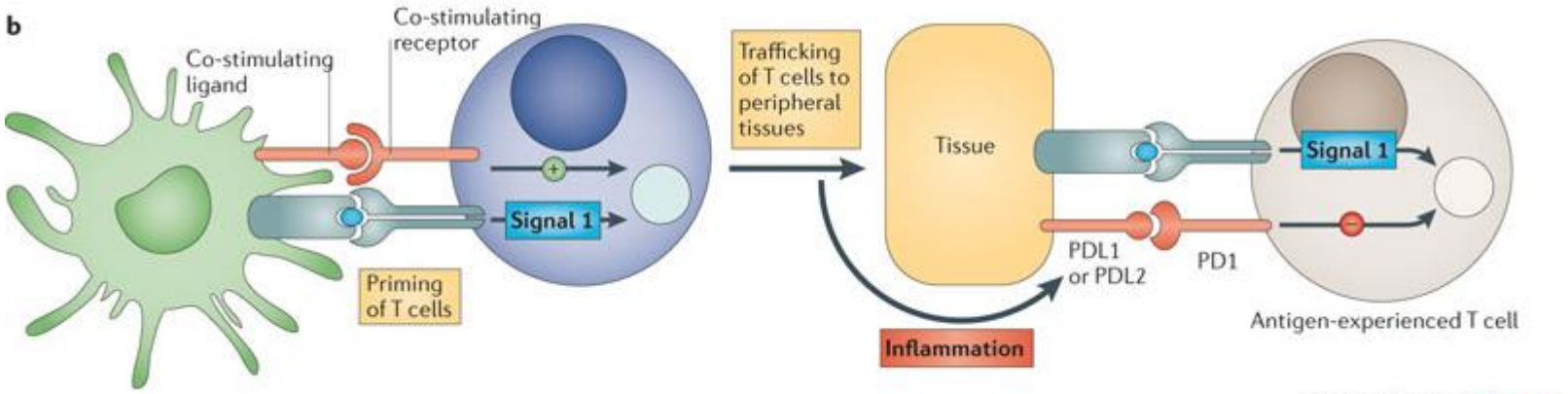
CTLA-4



Pardoll 2012

- Naïve and memory T cells express surface CD28
- CTLA-4 is transported to the surface in correlation to the strength of CD28 stimulation
- CTLA-4 also competes with higher affinity for CD80/86
- A dampening effect on downstream processing
- Constitutively present on T_{reg} cells

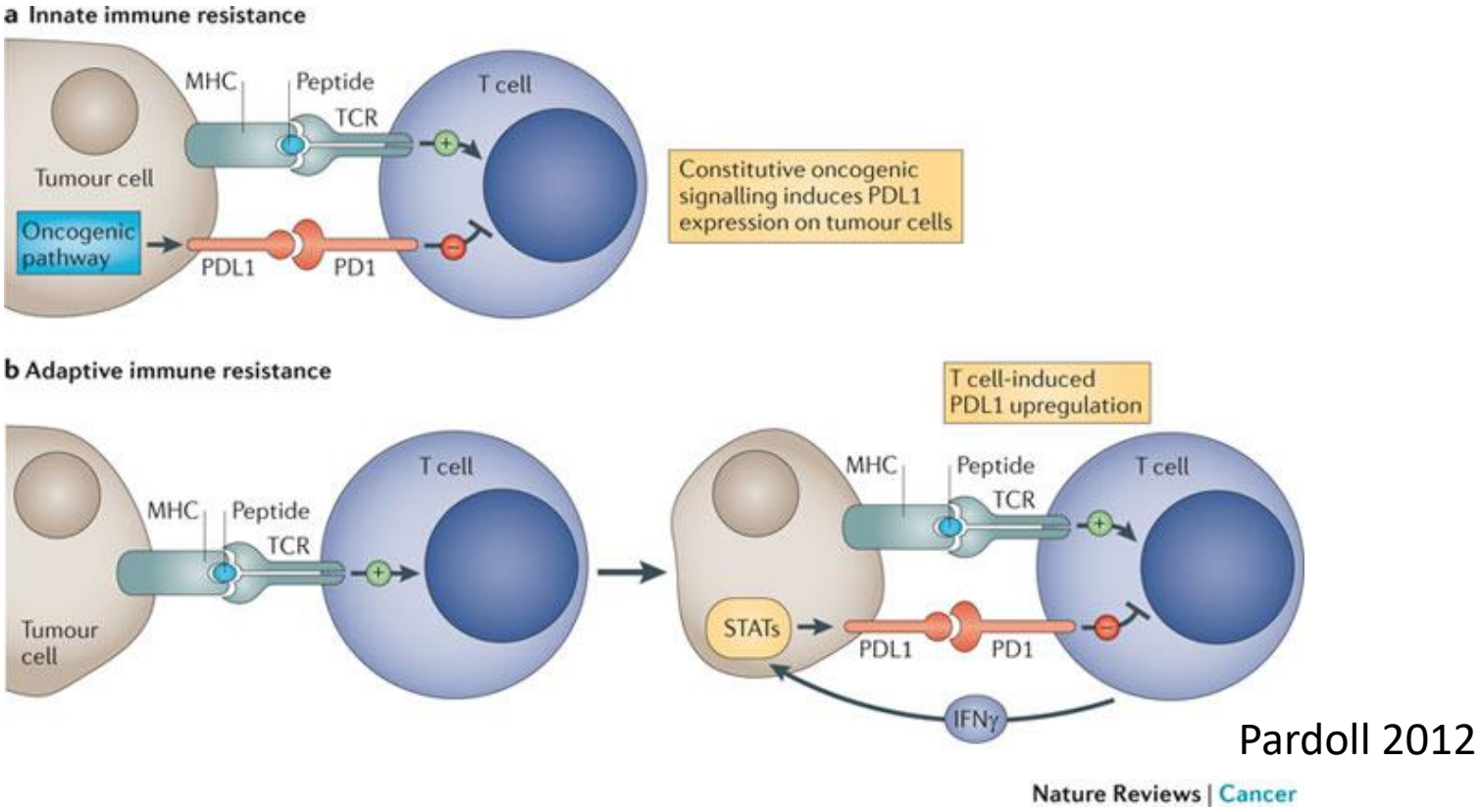
PD-1



Pardoll 2012

- A primed T-cell is heading to peripheral tissue to engage a target, and once activated begin to express PD-1
- Inflammation present in the tissue can promote upregulation of the ligands of PD-1
- In general, this limits collateral damage during cell-mediated destruction of infection

PD-1/PD-L1 in cancer



Pardoll 2012

- Cancer cells can increase the amount of PD-L1
- Successful T-cell tumor destruction can increase PD-L1 through upregulation in response to IFNγ

Checkpoint Blockade

- Where to start?
- Tumors known to respond to other immunotherapy

- **Melanoma**
- Estimated 9,320 deaths/year in US
- Metastatic disease 20% 5 yr survival
- Interleukin-2 durable *cure* in 4%

- **Renal Cell Cancer**
- Estimated 14,970 deaths/year in US
- Metastatic disease 12% 5 yr survival
- Interleukin-2 durable *cure* in 7%

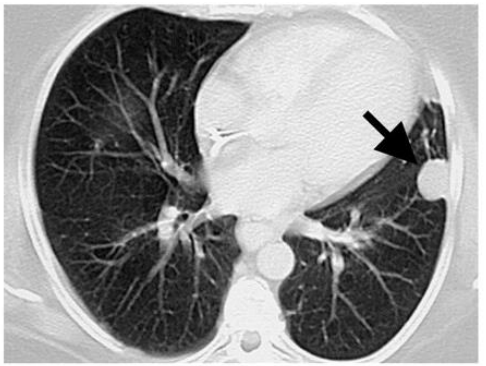
Smith FO Clin Cancer Res 2008

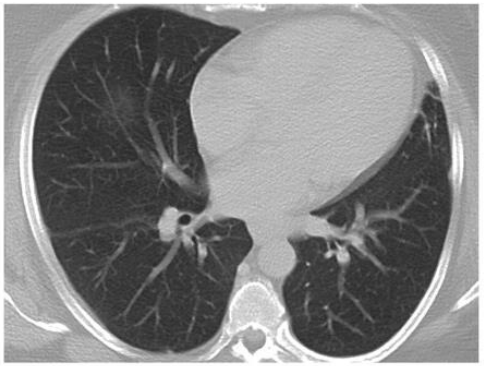
Klapper JA Cancer 2008

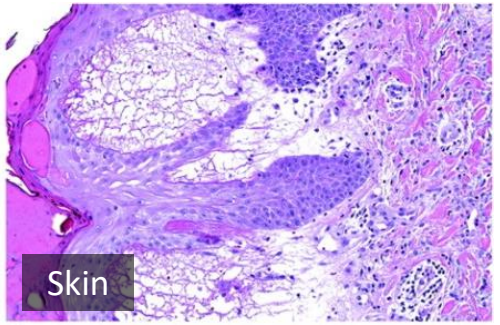
American Cancer Society Facts and Figures 2018

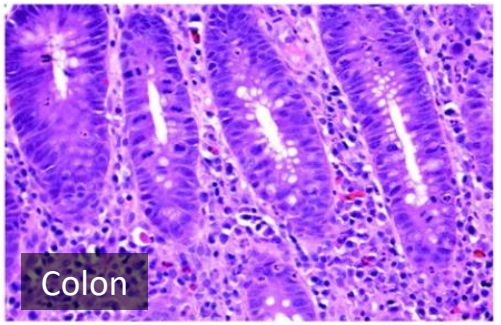
Checkpoint Blockade @ NCI

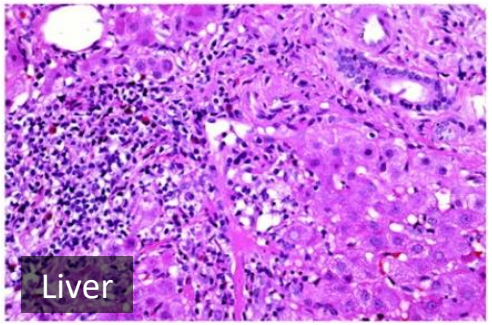
- αCTLA-4, ipilimumab
- Phase I trial
- mAb (3mg/kg) + peptide
- Enrolled 14 patients
- 2 complete responders
- 1 partial response
- Accrual stopped for toxicity
  - Dermatitis, colitis, hepatitis, hypophysitis (not pictured)

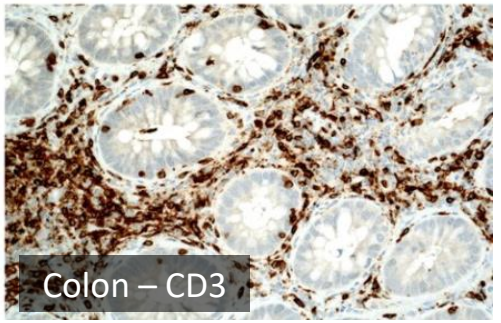












Phan GQ 2003 PNAS

Checkpoint Blockade @ NCI

- Cautiously proceeded with Phase II trials in melanoma and RCC, initially with dose reduction (3 → 1 mg/kg)
- Objective response was associated with development of autoimmune events

Melanoma, p=0.008

	> Gr 3 AE	< Gr 3 AE
Objective Response (CR = 2)	5 (36%)	2 (5%)
Non-responder	9	40

Attia P 2005

RCC, p=0.009

	> Gr 3 AE	< Gr 3 AE
Objective Response (CR = 0)	5 (29%)	0 (0%)
Non-responder	12	23

Yang JC 2007

Checkpoint Blockade @ NCI

- Formal Phase II intra-patient dose escalation demonstrated association of response with immune-related adverse events of any grade
- Enterocolitis was the most common grade 3/4 IRAE in patients with melanoma (18%) or RCC (28%)
- The administration of steroids to manage IRAE did not truncate responses

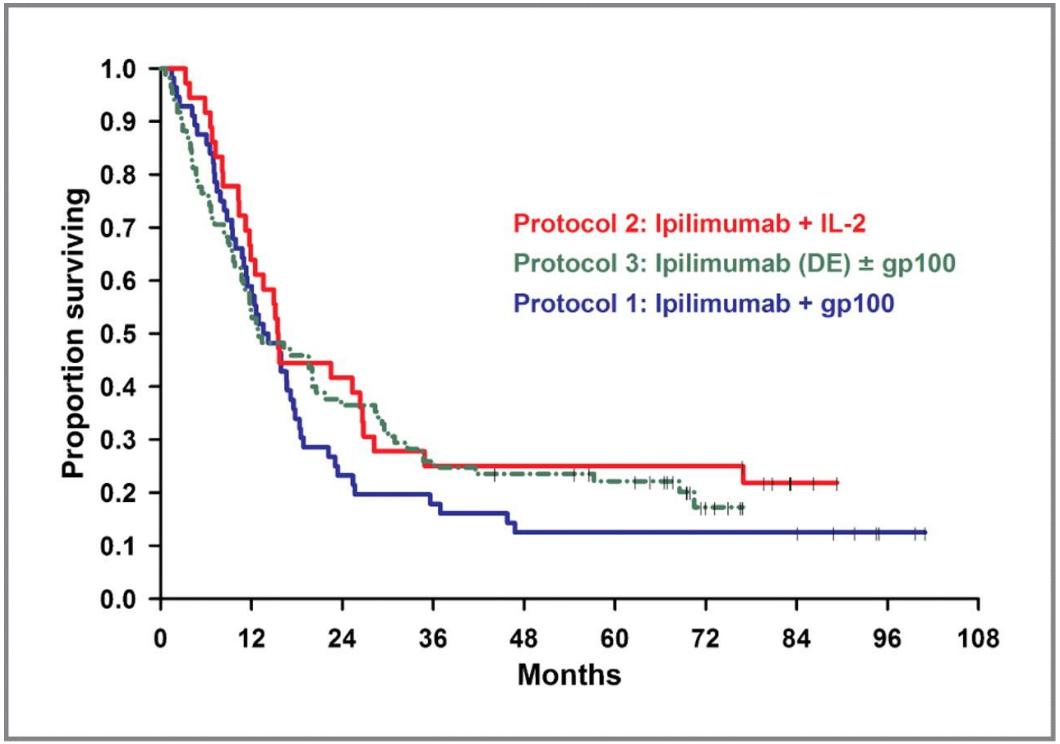
Melanoma, p=0.0004

	Gr 3/4 IRAE	Gr 1/2 IRAE	No IRAE
Objective Response (CR = 3)	14 (28%)	8 (22%)	1 (2%)
Non-responder	36	28	52

Beck KE 2006
Downey SG 2007

Checkpoint Blockade @ NCI

- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
  - OR 13-20%
  - 5 yr OS 13-23%

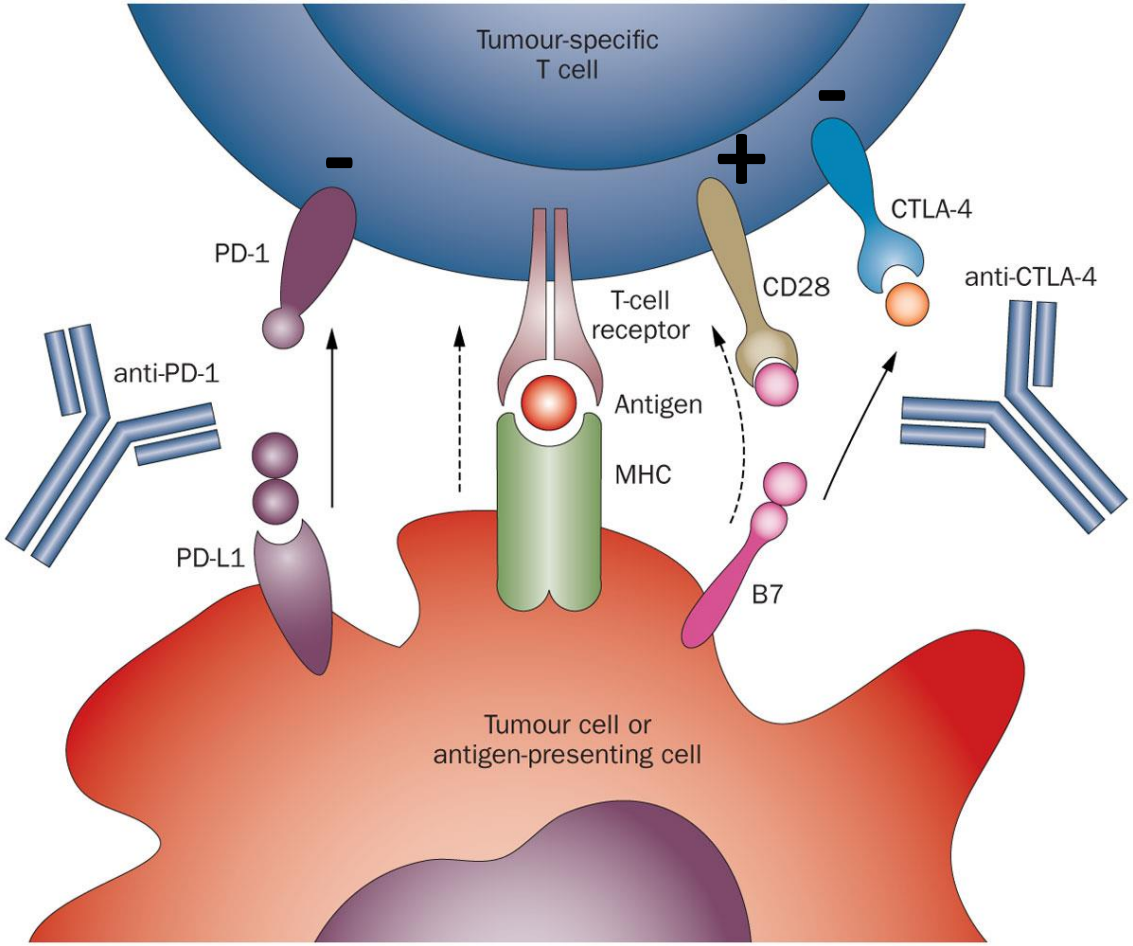


Prieto PA 2012

Clinical Cancer Research
AACR American Association for Cancer Research

Initial FDA approvals

Nivolumab
Pembrolizumab
2014



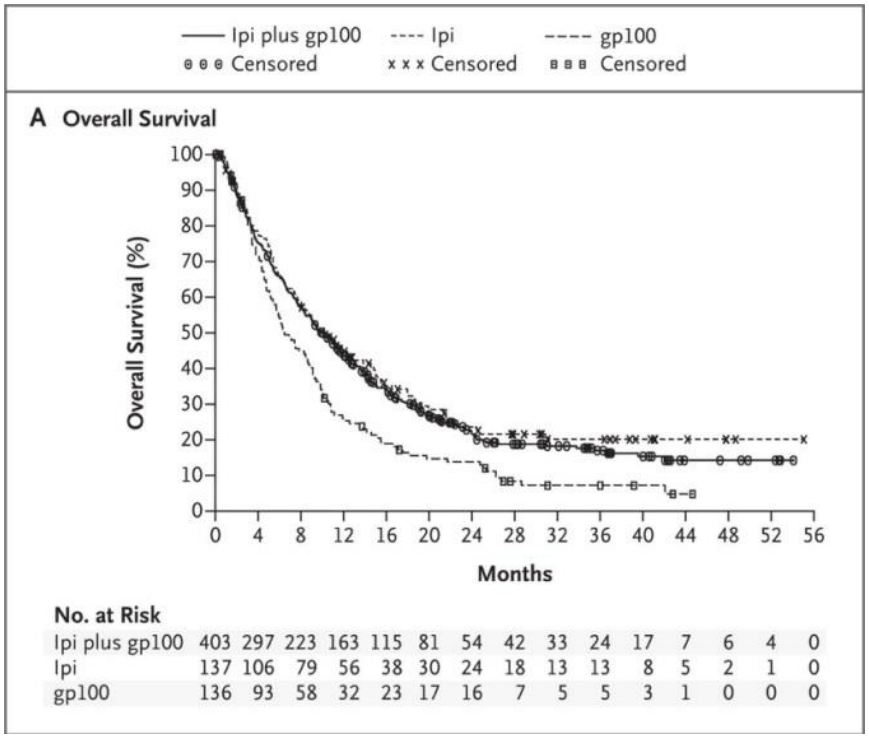
Ipilimumab
2011

Drake C 2013

nature REVIEWS CLINICAL ONCOLOGY

Ipilimumab for melanoma

- 11% response rate in Phase II trials at highest doses (10 mg/kg)
- Randomized Phase III ipilimumab ± gp100 vaccine vs. gp100 vaccine
- Allowed re-induction
- OR: ipilimumab arms
  7% (38/540)
  CR in 3 patients
- Disease control rate 22%
- Gr 3/4 irAE 10-15%



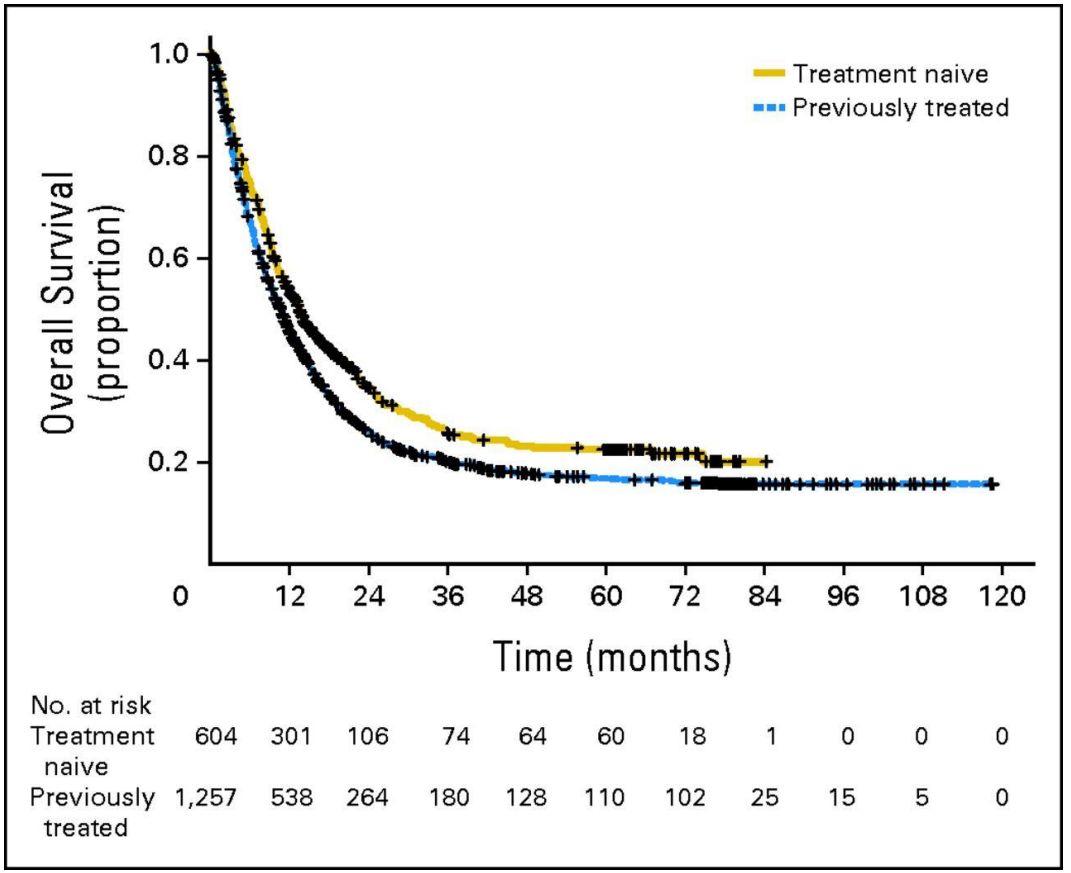
FDA approval for metastatic melanoma in March 2011

Hodi FS 2010

The NEW ENGLAND JOURNAL of MEDICINE

Ipilimumab for melanoma

- Updated survival
- 3 year OS, 20-26%
- "Tail of the curve"
  - Durable for a small # of patients

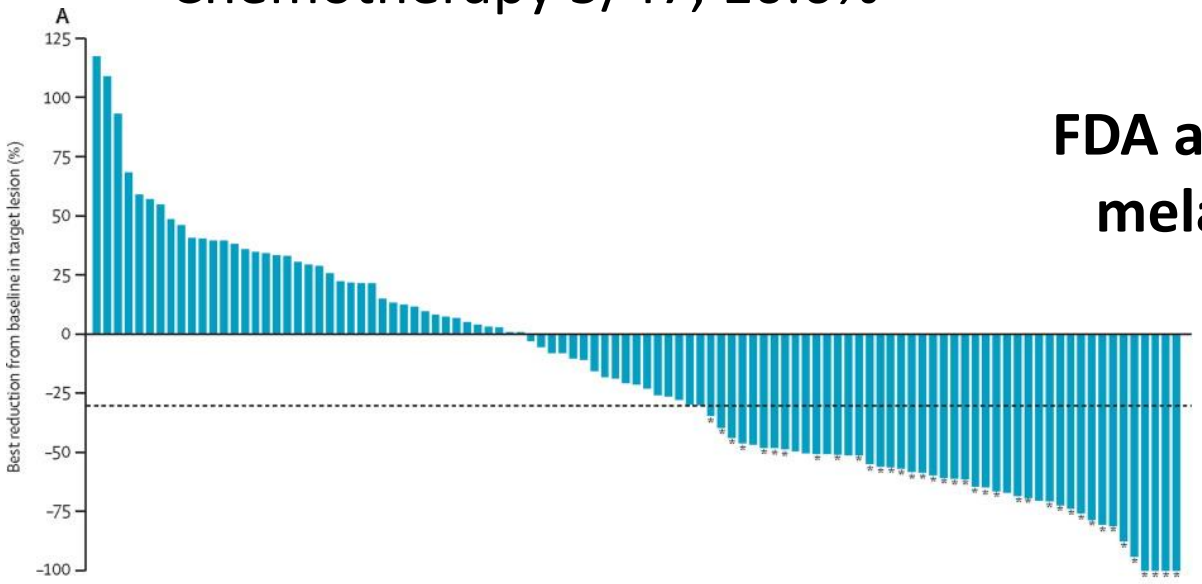


Schadendorf D 2015

Journal of Clinical Oncology®

Nivolumab for melanoma

- Ipilimumab-refractory
- RCT: nivolumab vs chemotherapy of choice (CheckMate 037)
- Objective Response
  - Nivolumab 38/120, 31.7% with 4 CR
  - Chemotherapy 5/47, 10.6%



FDA approval for refractory melanoma in December 2014

Weber JS 2015

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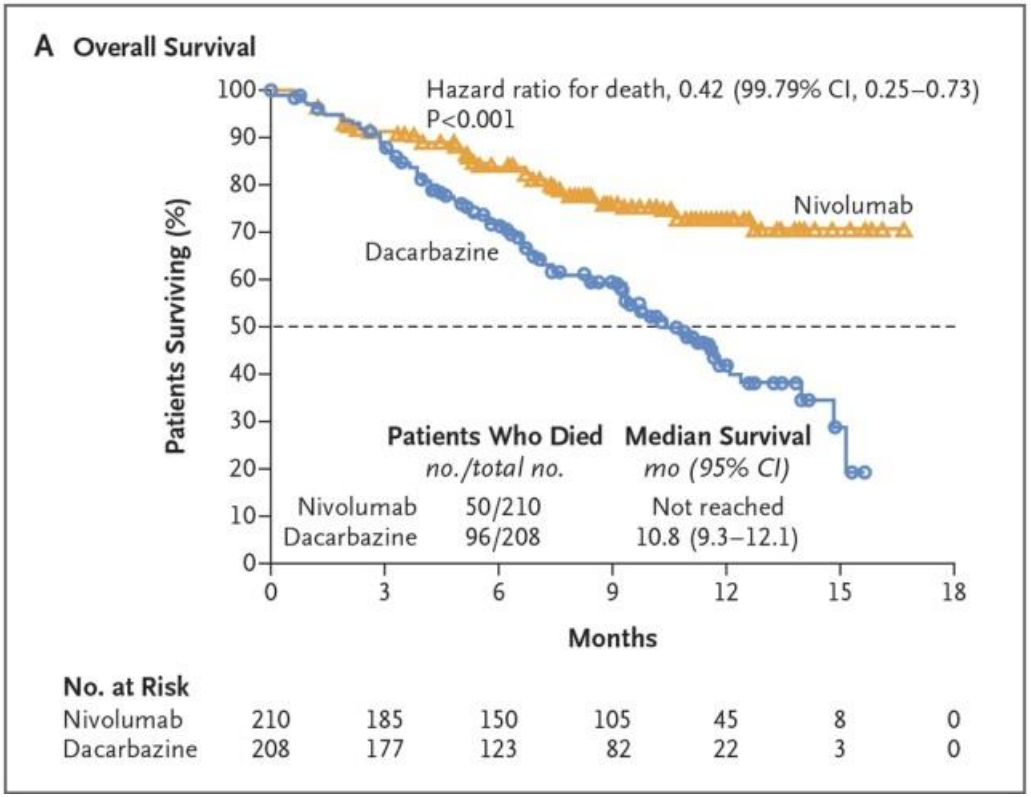
Nivolumab for melanoma

- Untreated metastatic disease
- Wildtype *BRAF*
- RCT: nivolumab vs dacarbazine (CheckMate 066)
- Objective response
  - Nivolumab 84/210 (40%)
    CR in 16 pts (7.6%)
  - Dacarbazine 29/208 (14%)
    CR in 2 pts (1%)



Approved for initial treatment (*BRAF*-wt) in November 2015

Robert C 2015

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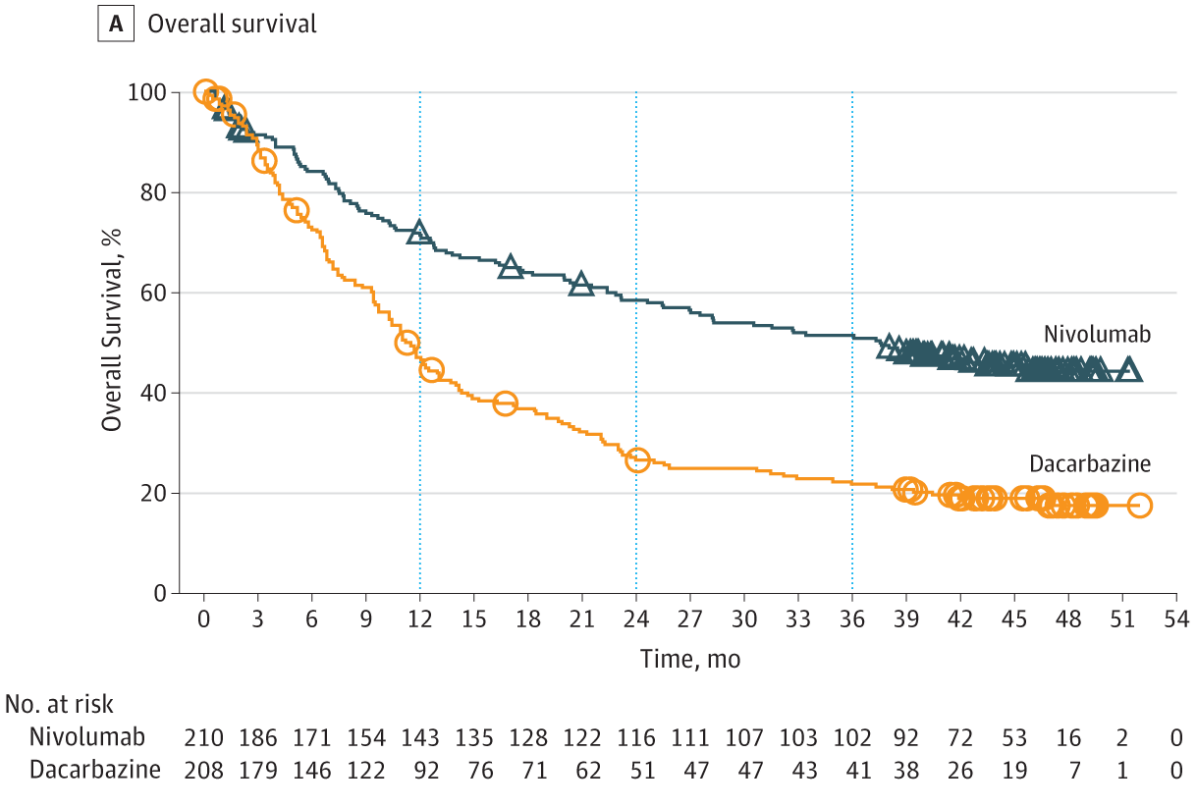
Nivolumab for melanoma

- Overall Survival update for Checkmate 066
- Three-year OS:
  - Nivolumab 51%
  - Dacarbazine 22%

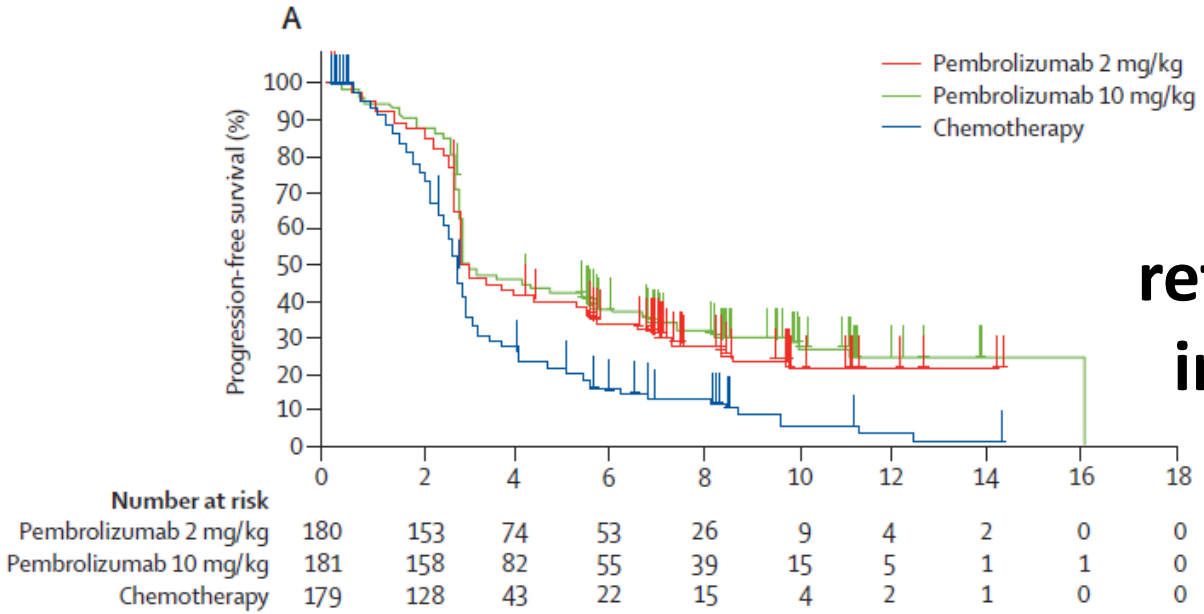


Ascierto P 2018

JAMA Oncology

Pembrolizumab for melanoma

- Ipilimumab-refractory
- Phase II, dose comparison (2mg/kg vs 10 mg/kg) vs chemo
- 540 patients
  - 2mg/kg ORR 38 (21%), 10 mg/kg ORR 46 (25%), chemo 8 (4%)
- Grade 3/4 AE 12%



FDA approval for refractory melanoma in September 2014

Ribas A 2015

THE LANCET Oncology

Pembrolizumab for melanoma

- RCT, KEYNOTE-006, first-line therapy
- Pembrolizumab (q2w, q3w) vs ipilimumab
- 1:1:1
- 834 patients
- Objective Response
  - Pembrolizumab q2w 94/279 (33.7%), CR 14
  - Pembrolizumab q3w 91/277 (32.9%), CR 17
  - Ipilimumab 33/278 (11.9%), CR 4

Robert C 2015

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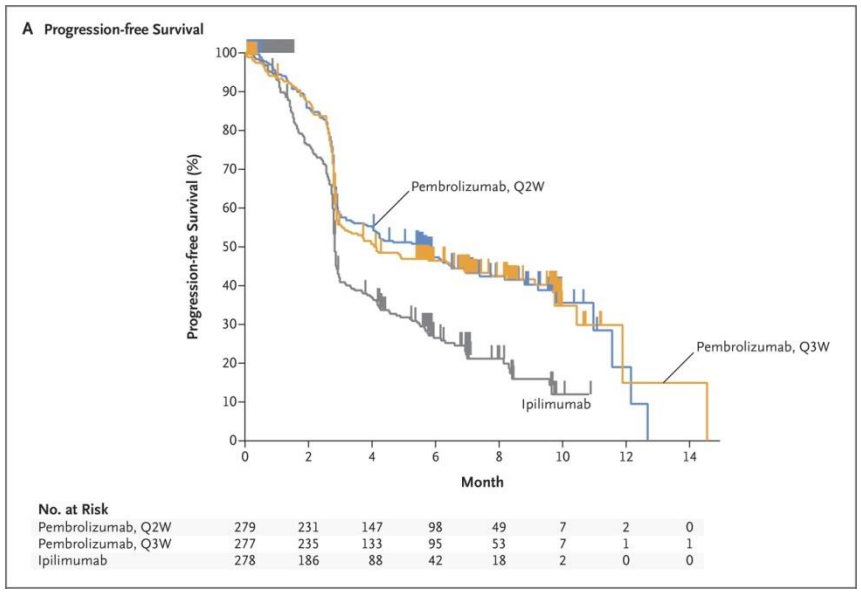
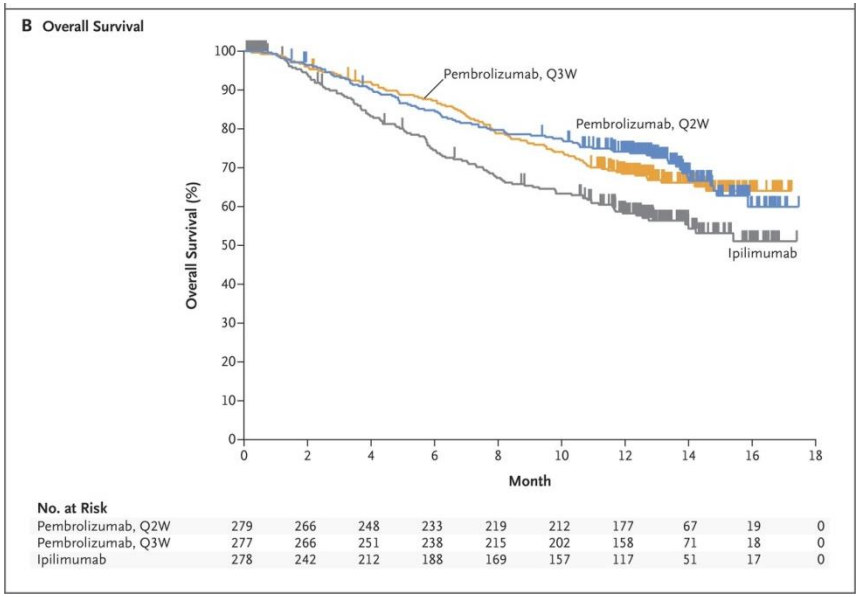
Pembrolizumab for melanoma





- Grade ≥3 AE
  - Pembrolizumab q2w 13.3% (1.4% Colitis)
  - Pembrolizumab q3w 10.1% (2.5% Colitis)
  - Ipilimumab 19.9% (7% Colitis)

Front-line FDA approval for melanoma in December 2015

Robert C 2015

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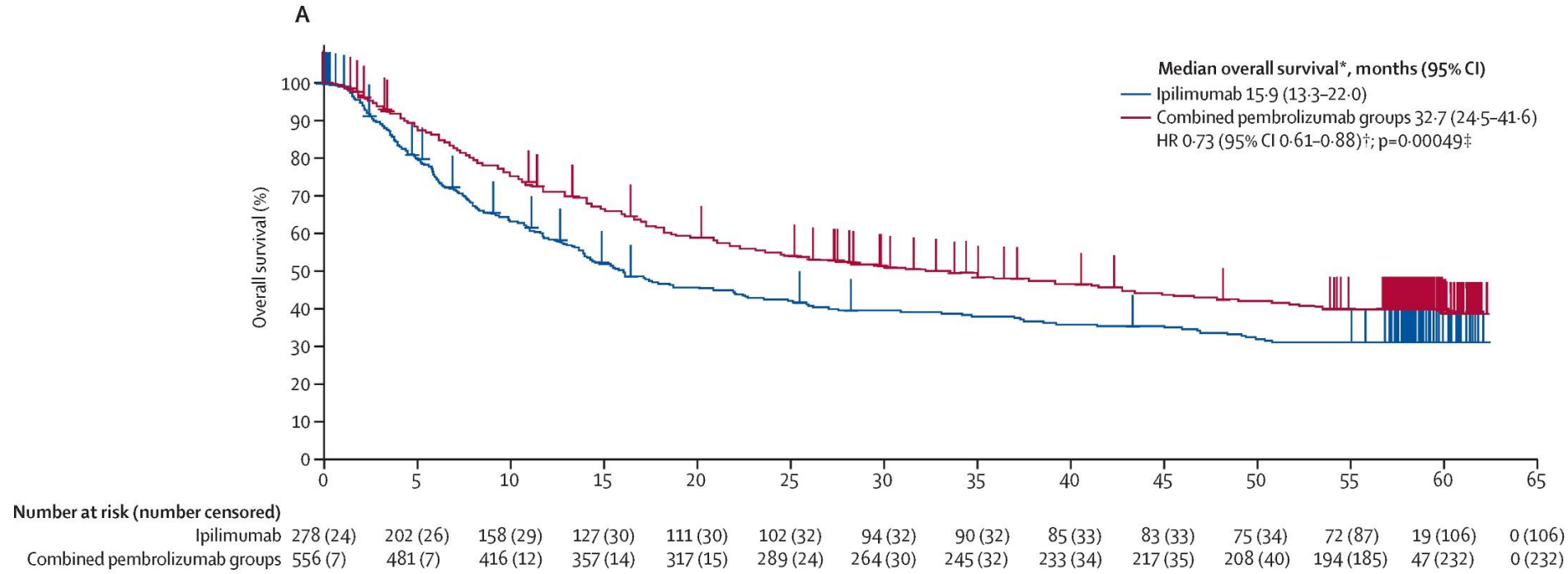
Pembrolizumab for melanoma

- Three year OS of 48.1% vs 37.8%



Robert C 2019

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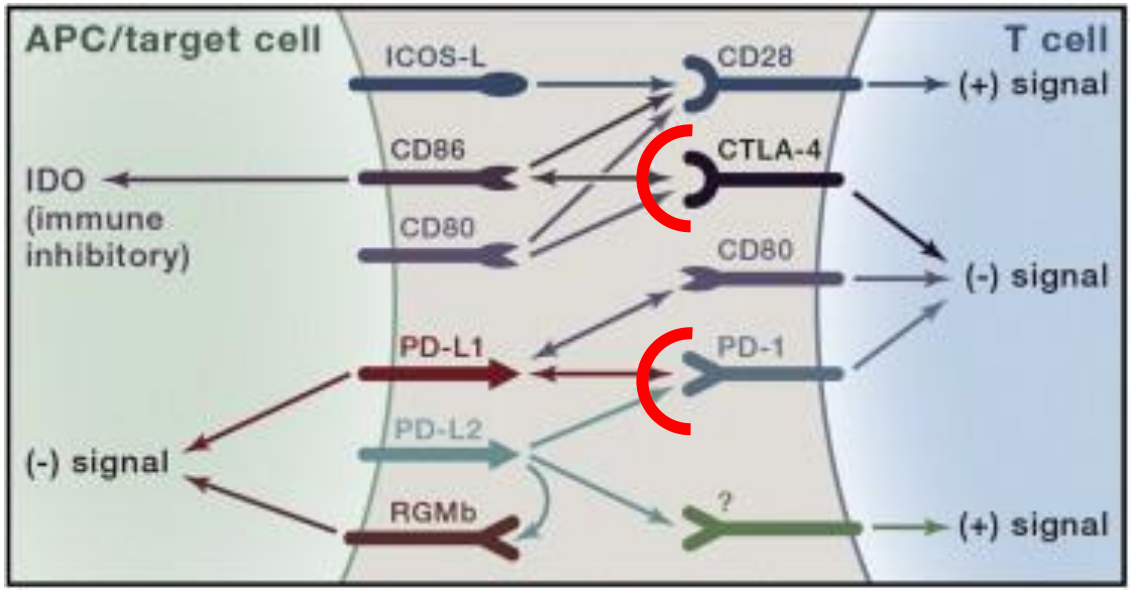
Checkpoint Modulation



Topalian, Cancer Cell 2015

- In melanoma, the two approved antibodies interfere with separate receptor/ligand complexes
- Could combination therapy improve response or survival?

Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1
- PD-L1 (+) ≥5%

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)	Total (N=945)
PD-L1 status — no. (%)				
Positive	80 (25.3)	68 (21.7)	75 (23.8)	223 (23.6)
Negative	208 (65.8)	210 (66.9)	202 (64.1)	620 (65.6)
Could not be determined or evaluated	28 (8.9)	36 (11.5)	38 (12.1)	102 (10.8)
BRAF status — no. (%)				
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

Larkin J 2015

Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1

- Grade 3/4 AE
  - Nivolumab 16.3%
  - Ipilimumab 27.3%
  - Combo 55.0%

Table 2. Response to Treatment.

Variable	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)
Best overall response — no. (%)*			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response†			
No. of patients with response	138	181	60
% of patients (95% CI)	43.7 (38.1–49.3)	57.6 (52.0–63.2)	19.0 (14.9–23.8)
Estimated odds ratio (95% CI)‡	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.001	<0.001	—
Time to objective response — mo			
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

* The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Data included patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted with the use of a two-sided Cochran–Mantel–Haenszel test stratified according to PD-L1 status, *BRAF* mutation status, and metastasis stage.
‡ The comparison is with the ipilimumab group.

Larkin J 2015

Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1

- Grade 3/4 AE
  - Nivolumab 21%
  - Ipilimumab 28%
  - Combo 59%

Table 1. Response to Treatment.*

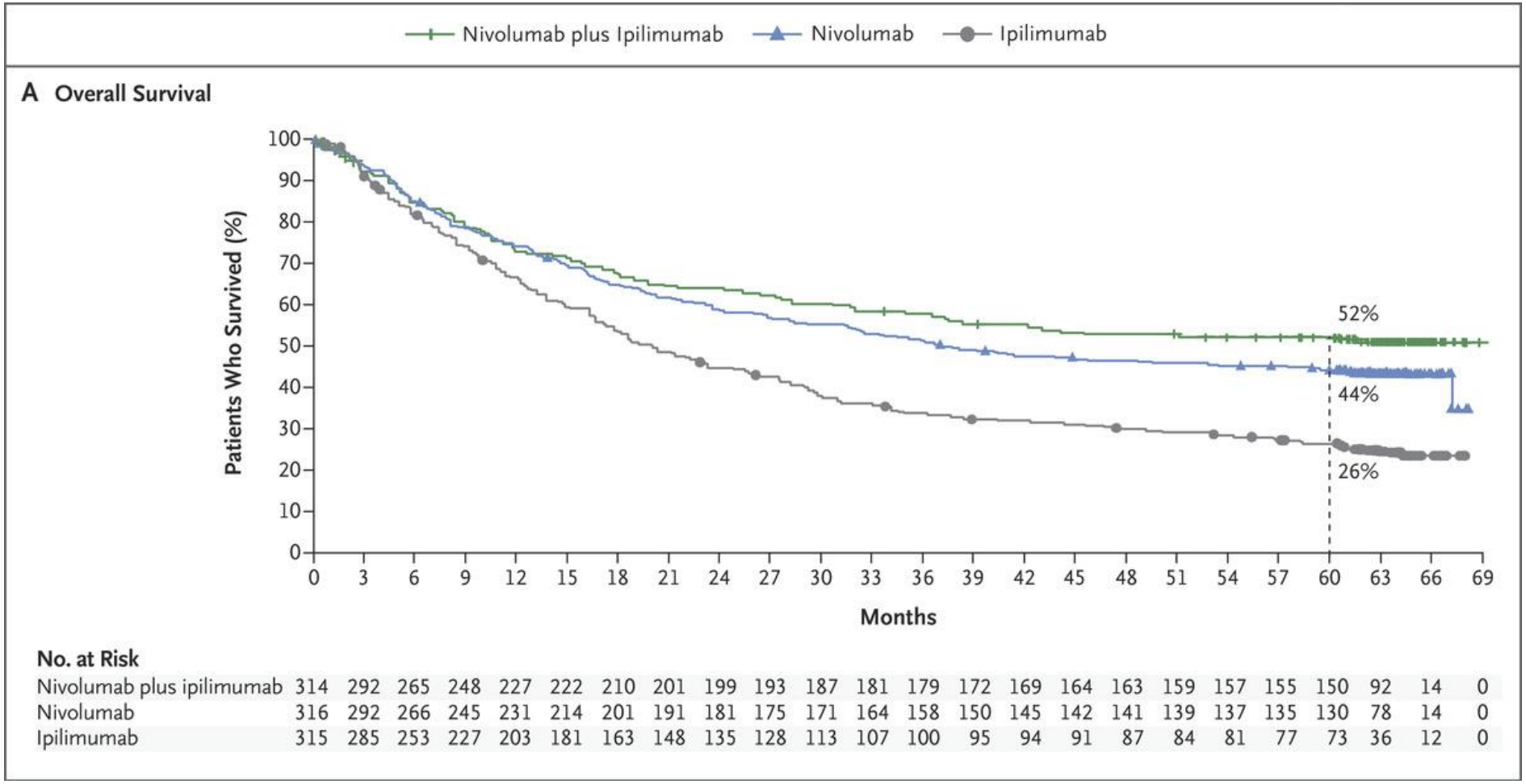
Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	61 (19)	52 (16)	16 (5)
Partial response	122 (39)	88 (28)	43 (14)
Stable disease	38 (12)	31 (10)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	28 (9)
Objective response‡			
No. of patients with response	183	140	59
% of patients (95% CI)	58 (53–64)	44 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.46 (4.45–9.38)	3.57 (2.48–5.15)	—
P value	<0.001	<0.001	—
Median duration of response (95% CI) — mo	NR	NR (36.3–NR)	19.3 (8.3–NR)

FDA approval of combination for melanoma in January 2016

Wolchok J 2017

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab/Ipilimumab for melanoma



Larkin J 2019

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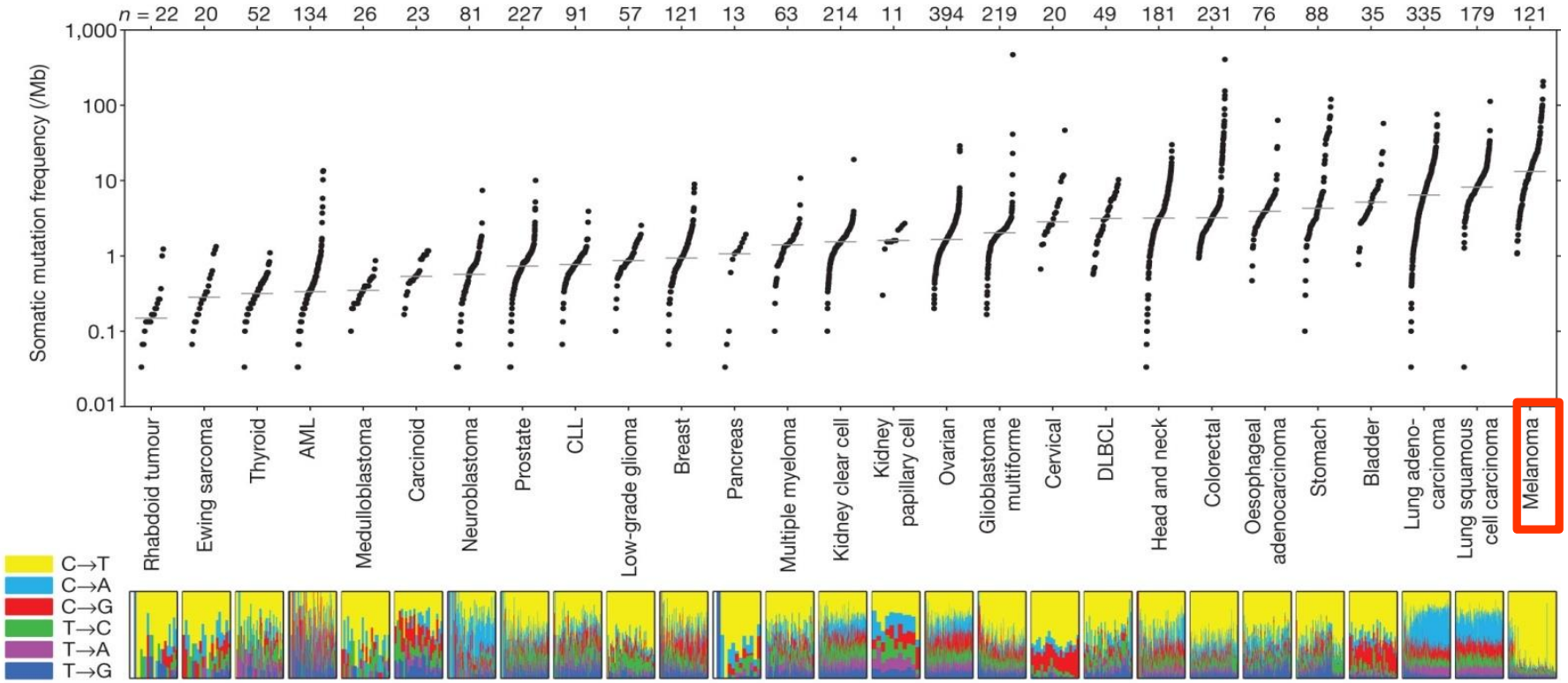
Why melanoma?



Lawrence MS 2013

nature
International weekly journal of science

Highly mutated tumors

- Non-small cell lung cancer (NSCLC)
  - ~154,050 deaths/year in US
  - Regional disease 29% 5 yr survival
  - Metastatic disease 5% 5 yr survival
  - Correlation between smoking and # mutations
- Bladder cancer
  - 17,240 deaths/year in US
  - Highly lethal once metastatic
- Tumors with mismatch repair (MMR) deficiency
  - Lynch syndrome (germline mutation)
  - Sporadic mutation
  - MSH2, MLH1, MSH6, PMS2

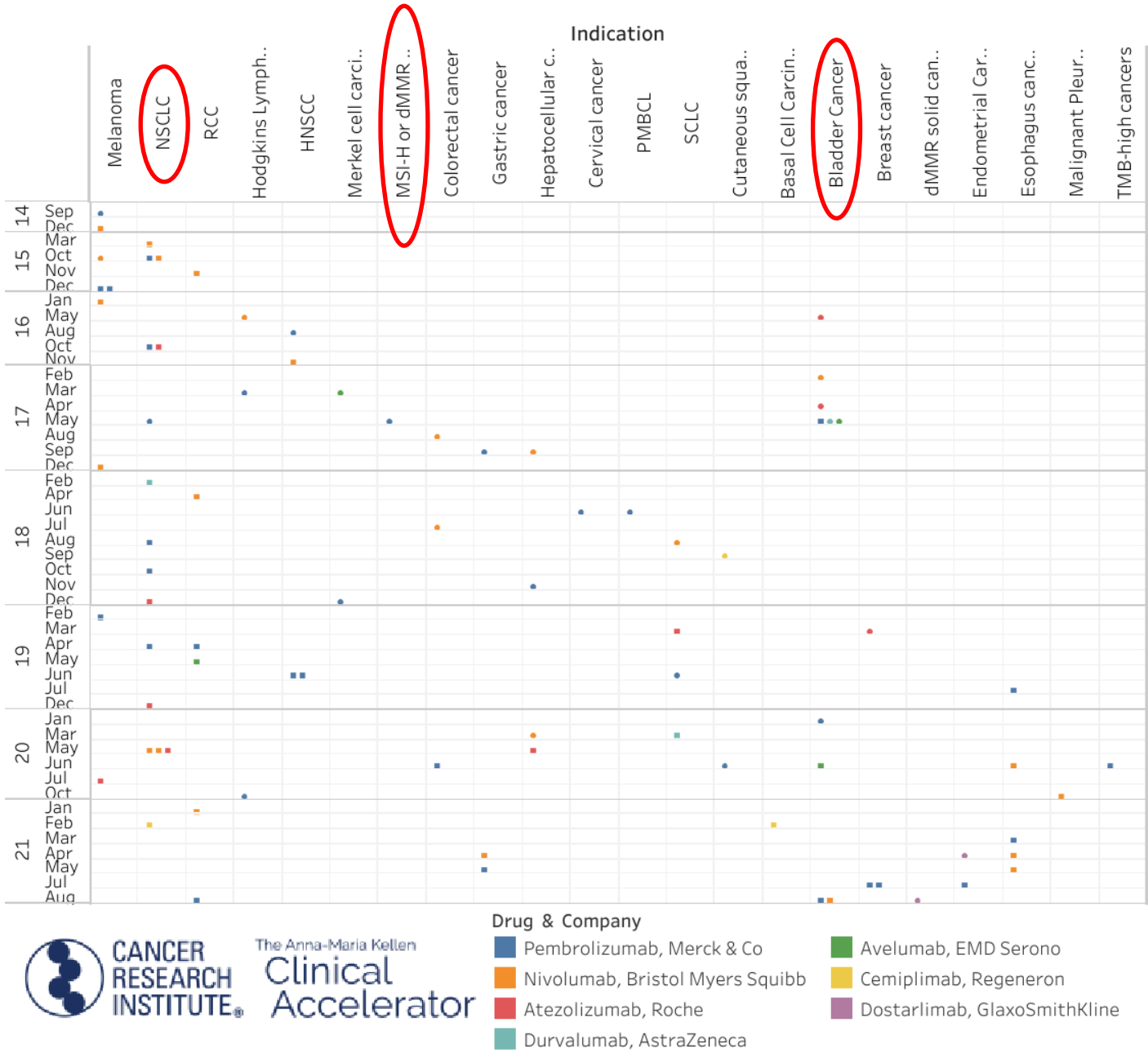
American Cancer Society Facts and Figures 2018

https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape

Timeline of Anti-PD-1/L1 Antibody Approvals by the FDA

Updated August 31, 2021

Sources: CRI, CRI Analytics, and FDA



CANCER RESEARCH INSTITUTE®

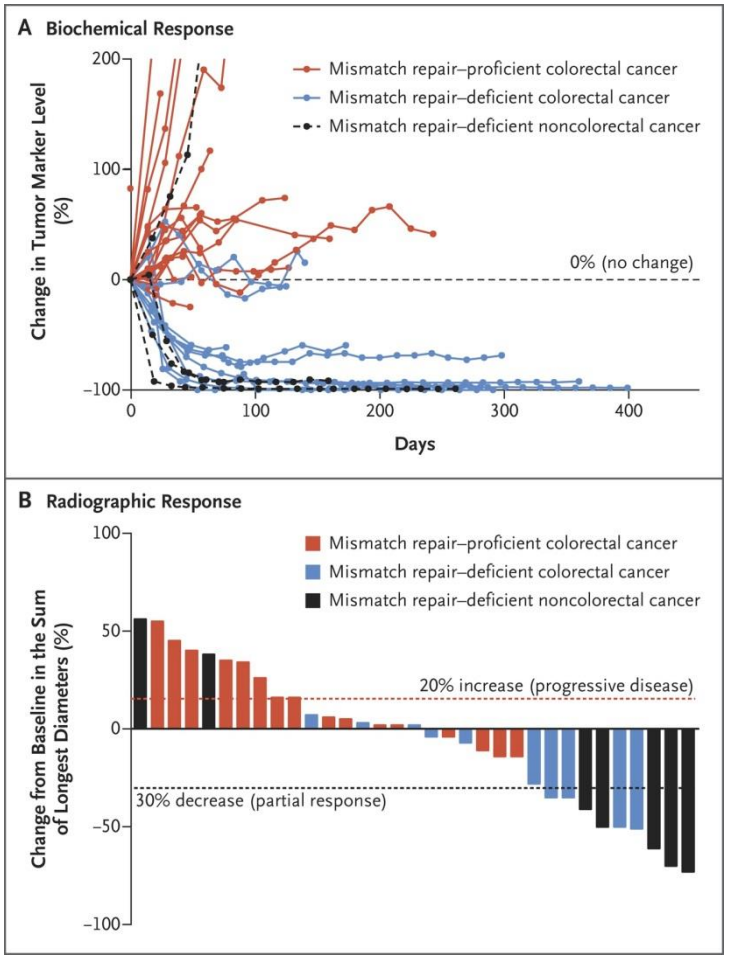
The Anna-Maria Kellen Clinical Accelerator

Drug & Company

- Pembrolizumab, Merck & Co
- Nivolumab, Bristol Myers Squibb
- Atezolizumab, Roche
- Durvalumab, AstraZeneca
- Avelumab, EMD Serono
- Cemiplimab, Regeneron
- Dostarlimab, GlaxoSmithKline

Pembrolizumab for mismatch repair deficient (dMMR) cancer

- Builds on hypothesis of neoantigens from somatic mutations
- Phase 2 study
- Three parallel cohorts
  - MMR-proficient CRC
  - MMR-deficient CRC
  - MMR-deficient other



Le DT 2015

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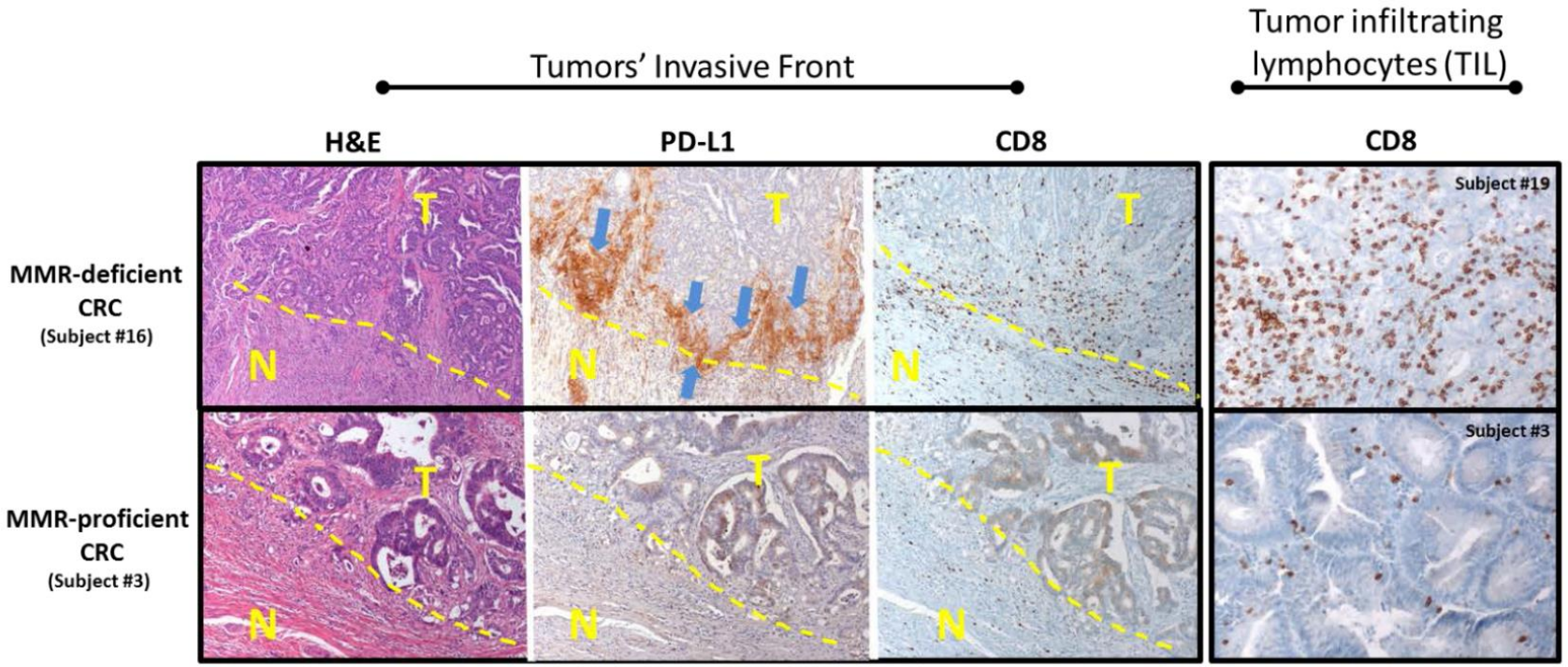
Pembrolizumab at the tumor-stroma interface



FDA approval for dMMR tumors in May 2017

Le DT 2015

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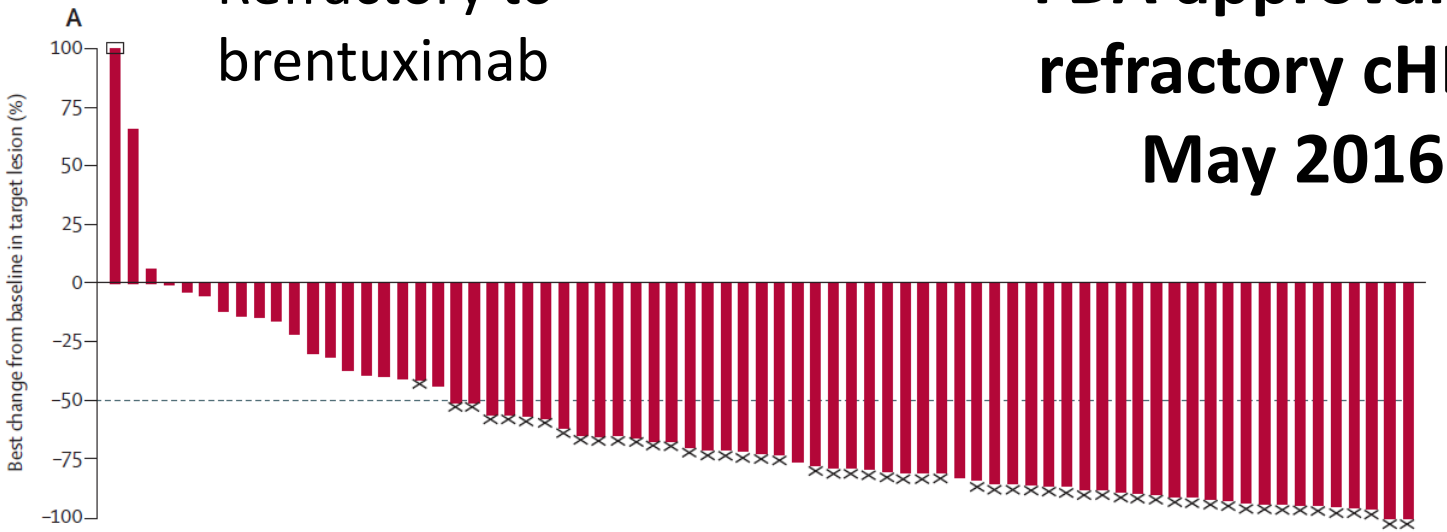
Checkpoint Blockade

- Highly mutated tumors
  - Melanoma
  - Non-small cell lung cancer
  - Bladder cancer
  - Tumors with mismatch repair deficiency
- Use in other tumors?
  - Renal cell
    - Responds to other immunotherapy
  - Hodgkin's lymphoma
    - Reed-Sternberg cells have elevated amounts of PD-L1
  - Head and neck SCC
    - HPV and mutations

Nivolumab for Hodgkin's Lymphoma

- 80 patients
  - Classical (cHL)
  - Refractory to stem cell transplant
  - Refractory to brentuximab
- Objective Response
  - 53/80 (66%)
  - 7 complete remission

FDA approval for refractory cHL in May 2016



Younes A 2016

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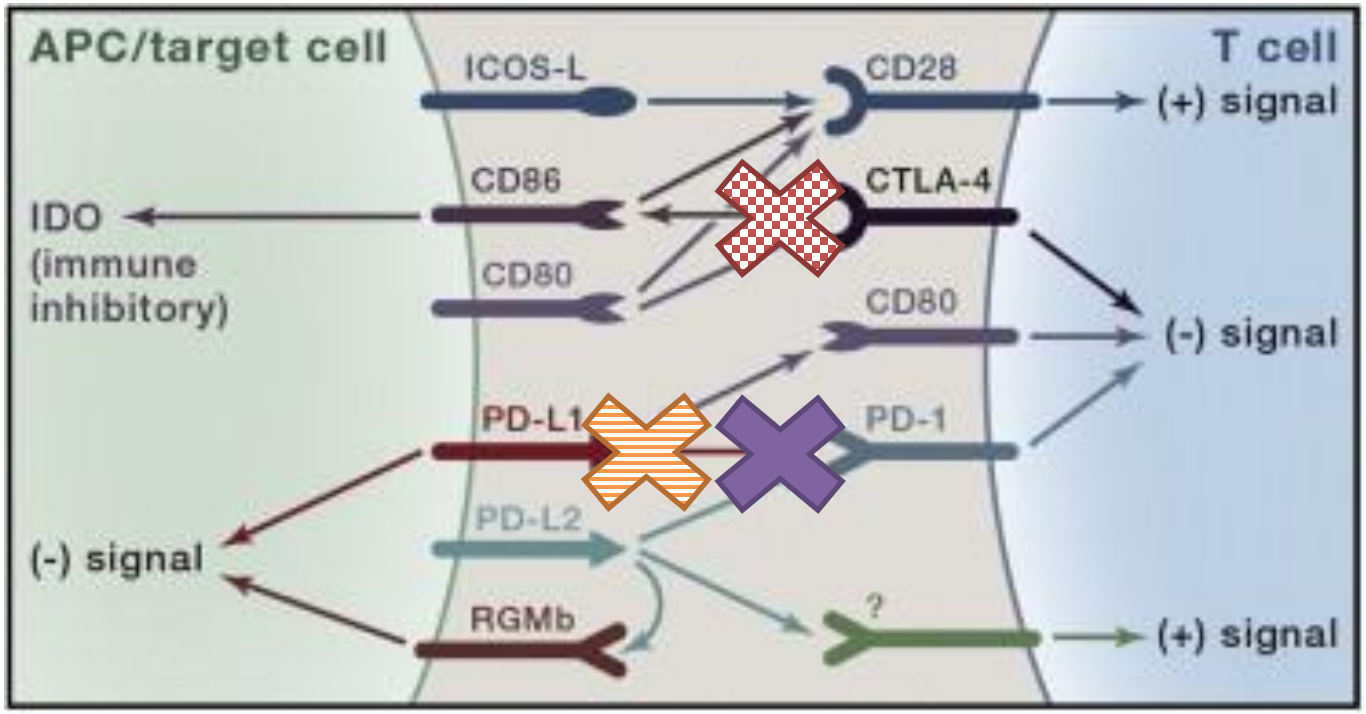
Checkpoint Modulation

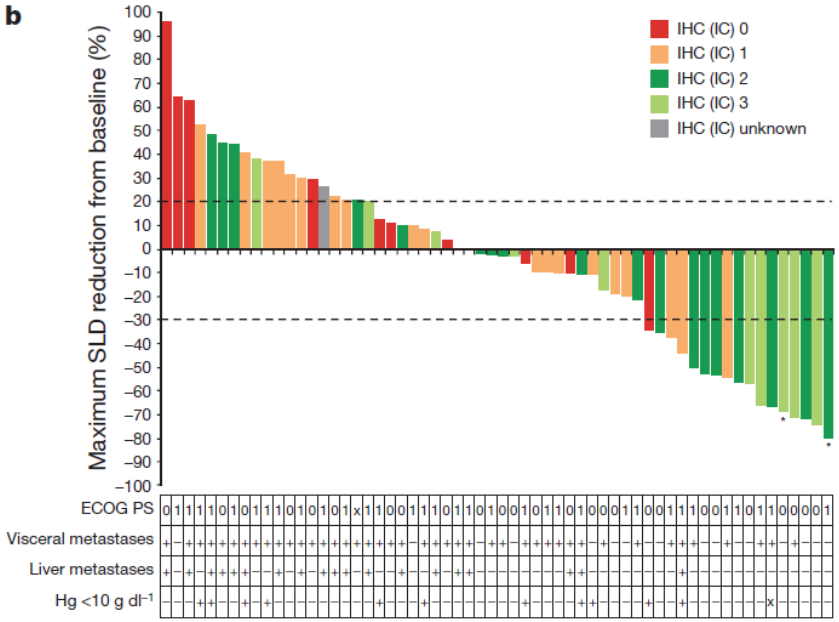


Topalian, Cancer Cell 2015

- Initial focus on blocking Signal 2 on the T cell side
  - Anti-CTLA-4: ipilimumab (Yervoy), tremelimumab
  - Anti-PD-1: nivolumab (Opdivo), pembrolizumab (Keytruda), cemiplimab (Libtayo)
- Newer development on blocking Signal 2 on the target
  - Anti-PD-L1: atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi)

αPD-L1 in Urothelial bladder cancer

- MPDL3280A
- Atezolizumab
- 15 mg/kg q3w
- 27% tumors with >5% PD-L1 by IHC
- 65 patients with pre-treatment biopsy
- Objective Response
  - ≥ 5% PD-L1 13/30 (43.3%)
  - < 5% PD-L1 4/35 (11.4%)
- Grade 3/4 AE 4%

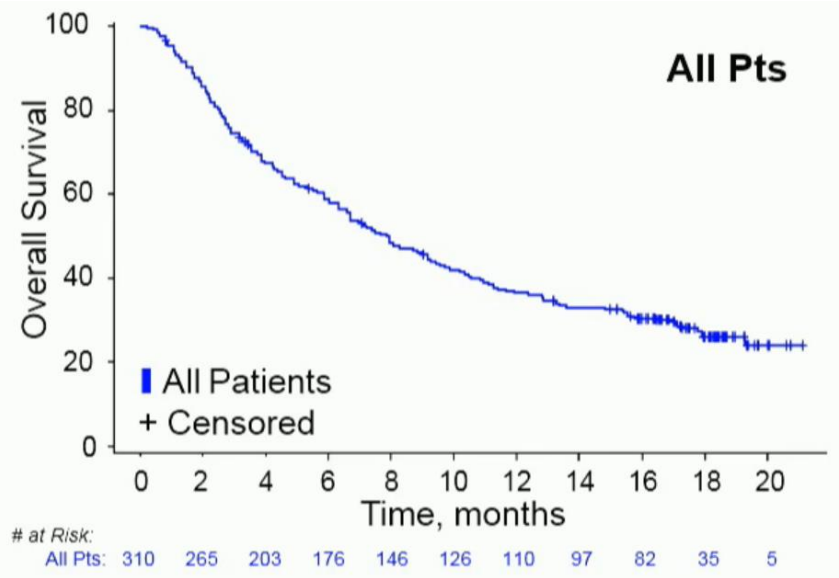


Powles T 2014

nature
International weekly journal of science

αPD-L1 in Urothelial bladder cancer

- 310 patients
- Objective Response
  - 45 (15%)
  - With 15 complete responses
- Overall Survival
  - 7.9 months
- 1 yr Survival
  - 37%



FDA approval for urothelial cancer in May 2016

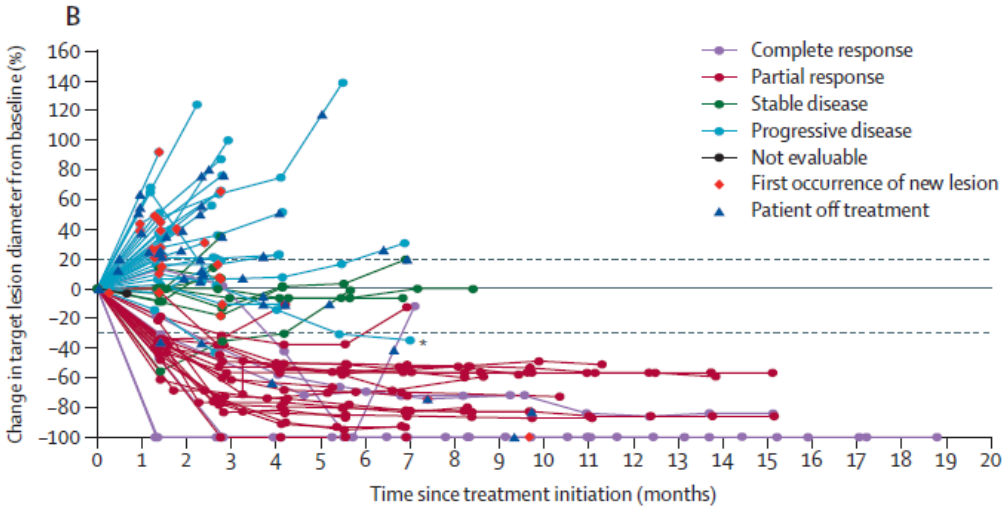
Rosenberg JE 2016 THE LANCET

Updated Dreicer R, 2016 ASCO

Avelumab in Merkel cell carcinoma

- Polyoma virus & UV damage
- 88 patients
  - Confirmed metastatic disease

- Objective Response
  - 28/88 (32%)
  - 8 complete remission



FDA approval for Merkel cell carcinoma in March 2017

Kaufman HL 2016

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Blocking the PD-1/PD-L1 pathway

	Drug	Melanoma	NSCLC	RCC	Bladder
Anti-PD-1	Nivolumab	32% (n=107)	17% (n=129) 30% (n=20)	29% (n=34) 21% (n=168)	20% (n=270)*[1]
	Pembrolizumab	38% (n=135) 26% (n=157)	26% (n=42) 20% (n=194)	-	24% (n=29)
Anti-PD-L1	Durvalumab	-	16% (n=58)	-	18% (n=191)*[2]
	Atezolizumab	30% (n=43)	23% (n=53)	14% (n=56)	26% (n=65)
	Avelumab*	-	-	-	18% (n=44)*[3]

OR % (size of trial)
*Added to original chart

FDA Approved

Adapted from Lipson 2015

Seminars in Oncology

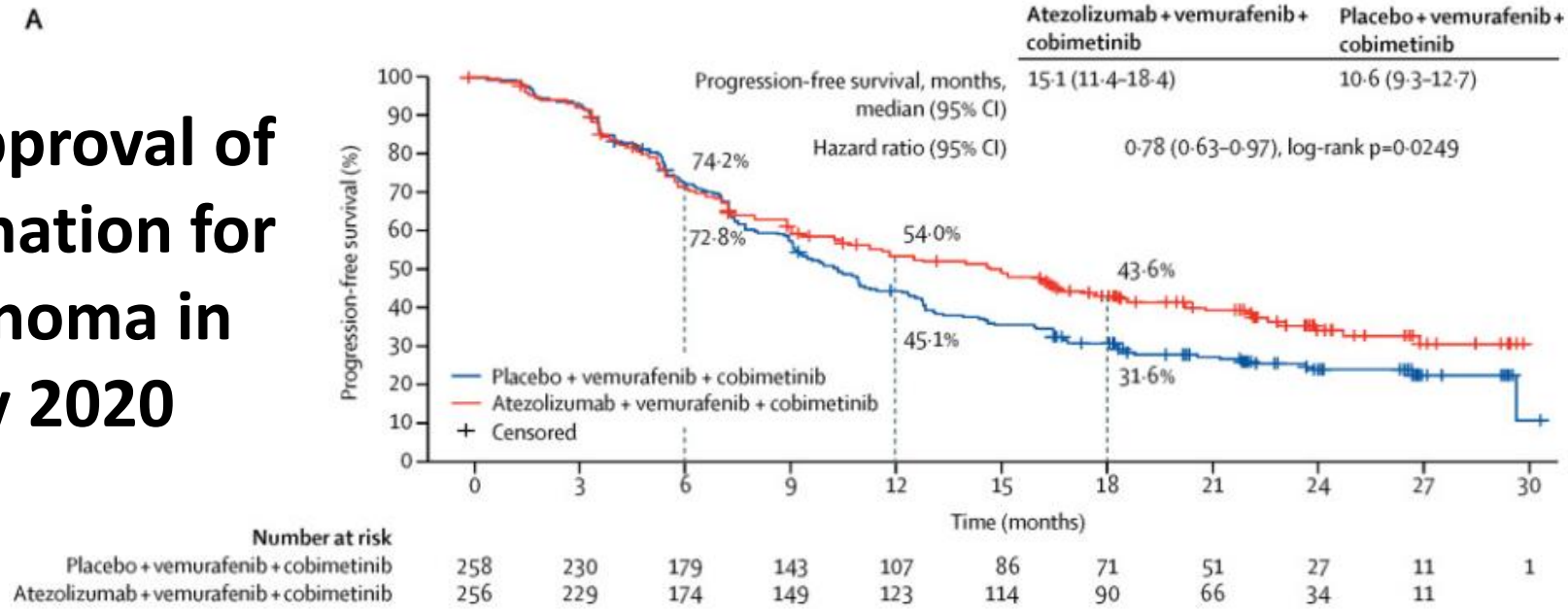
What about combinations?

[1] Sharma P Lancet Oncol 2017
[2] Powles T JAMA Oncol 2017
[3] Apolo A J Clin Oncol 2017

Atezolizumab (αPD-L1) for melanoma

- BRAF V600E/K mutation
- Phase III RCT, with BRAK/MEK inhibitors
- 514 patients, randomized 1:1

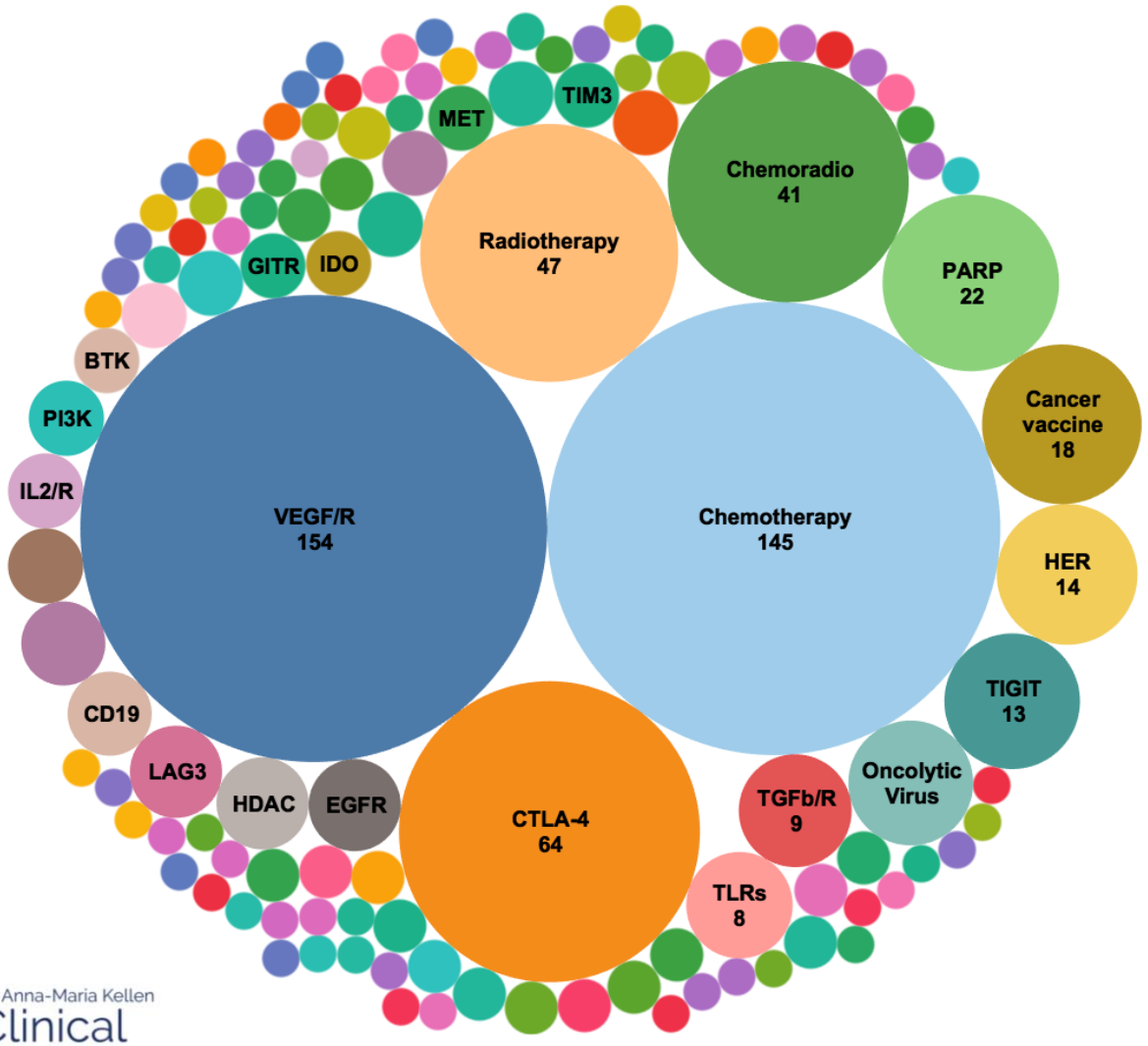
FDA approval of combination for melanoma in July 2020



Gutzmer R 2020 THE LANCET

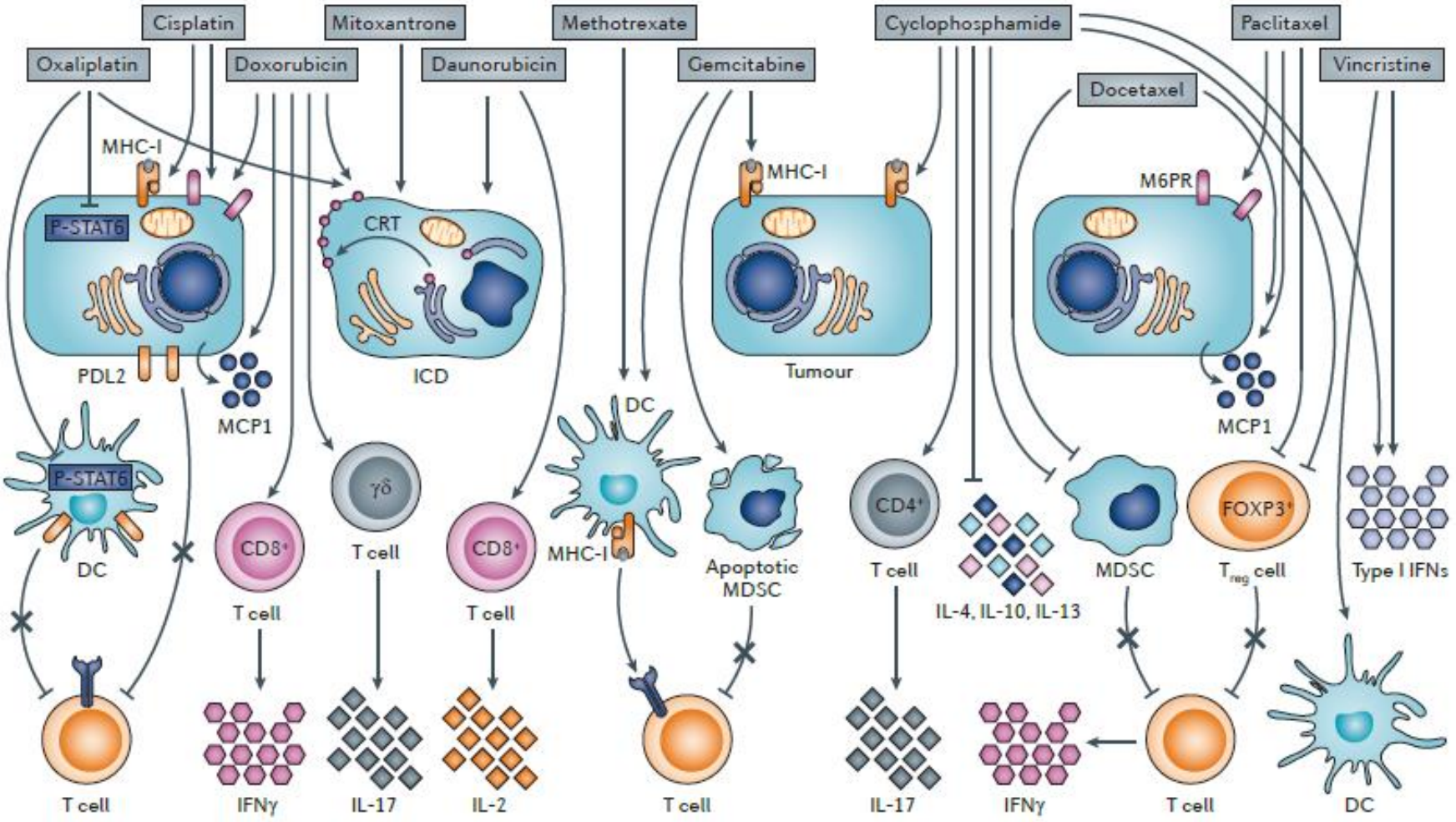
Combination Clinical Trials

- Over 2900 different trials of combination therapy with 253 different agents
- 724 new trials in first 9 months of 2020



CANCER RESEARCH INSTITUTE
The Anna-Maria Kellen Clinical Accelerator

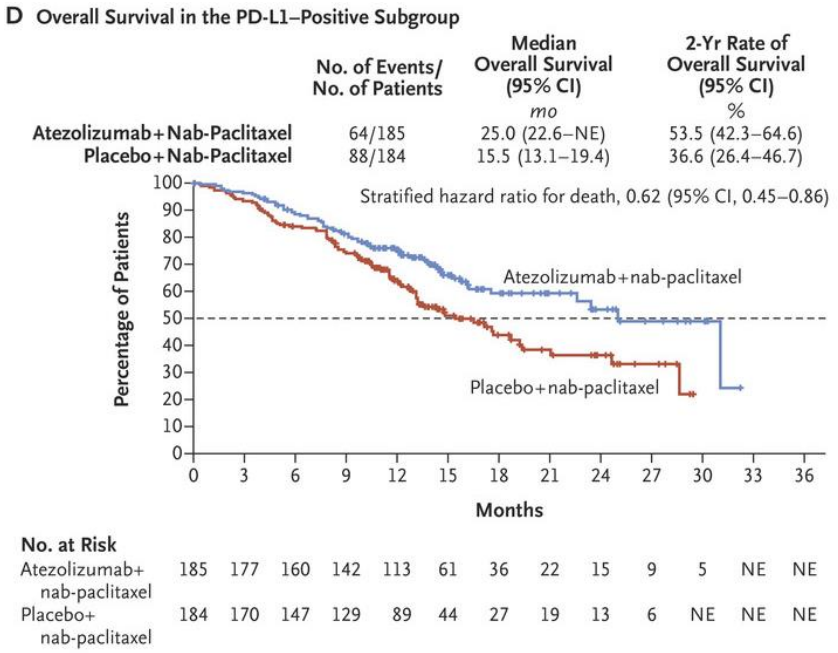
Rationale for Chemotherapy Combinations



Galluzzi Nature Reviews Drug Discovery (2012)

PD-L1/chemo in mBrCa

- Nab-paclitaxel ± atezolizumab
- 902 patients
- Randomized
- 379 with PD-L1+ (≥1%) tumors
- Objective Response
  - Chemo + atezo 59%
  - Chemo + placebo 43%
- 2yr Survival
  - Chemo + atezo 54%
  - Chemo + placebo 37%



FDA approval for PD-L1+ TNBC in March 2019

Schmid et al 2018

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Checkpoint Modulators

- Every expanding list of indications
- Any questions?